

Acid gastroesophageal reflux and intensity of symptoms in children with gastroesophageal reflux disease. Comparison of primary gastroesophageal reflux and gastroesophageal reflux secondary to food allergy

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ABSTRACT

The ability to differentiate between primary and secondary causes of gastroesophageal reflux (GER) is extremely important during the diagnostic procedure. At the same time, the quality of symptoms and the intensity of the course of gastroesophageal reflux disease (GERD) should be estimated. Acid GER is assessed using 24-hour esophageal pH monitoring; the results of this diagnostic test should always be interpreted alongside the clinical picture.

Purpose: To establish the interdependence between the intensity of the clinical symptoms and the acid reflux index in children with primary GER and GER secondary to cow's milk protein allergy (CMA) and/or other food allergies (FA).

Materials and Methods: A total of 138 children of various ages with symptoms of GERD were included in the study. The diagnostic procedure included 24-hour pH monitoring of the esophagus with a 2-channel probe (distal and proximal lead). For this purpose, ESPGAN diagnostic criteria were implemented. The type and intensity of typical manifestations of GERD were assessed with the help of our own scoring system. This diagnostic and therapeutic algorithm which includes an oral food challenge test, was applied to 138 children in order to differentiate primary GER from GER secondary to CMA/FA.

Results: Primary GERD was diagnosed in 76 patients (55.1%) with a mean age: $x=25.20$ months ± 27.28 (group 1) and GERD secondary to CMA/FA was confirmed in 62 children (44.9%) with a mean age: $x = 21.53$ months ± 17.79 (group 2). The most important pH-metric parameter analyzed in study groups 1 and 2 was the GER index: total and supine. An assessment of the intensity of symptoms and a comparative analysis of intensity was evaluated against the GER index: total and supine. Among study group 1, the following gradation of symptoms was found: in 31 children (40.8%) – degree 3, in 33 children (43.4%) – degree 4, and in 12 children (15.8%) - degree 5, whereas among the patients in group 2: 25 (40.3%) were in degree 3, 27 (43.6%) were in degree 4, and 10 (16.1%) were in degree 5. It was estimated that the higher the GER result in both total and supine positions (for both leads), the higher the level of symptoms noted. This interdependence was demonstrated for both groups.

Conclusions: In seeking to determine any etiopathogenetic connection between primary GER or GER secondary to CMA/FA and their clinical consequences, 24-hour esophageal pH monitoring with a 2-channel probe is recommended, since it provides for better clinical control of GERD and its appropriate treatment.

Key words: primary GER, GER secondary to CMA/FA, clinical manifestations, esophageal pH monitoring, immunoallergologic tests

INTRODUCTION

Acid gastroesophageal reflux (GER) is defined as a recurrent return of the stomach contents back up into the esophagus. gastroesophageal reflux disease (GERD) is diagnosed when

gastric contents, retrograding into the esophagus or even to the pharynx, cause particular symptoms: typical or atypical (outside the gastrointestinal system), mono- or multi-organ, in isolated or associated form (1-5).

It is vital to differentiate the cause of GER (primary vs. secondary cause) during the diagnostic procedure (6-9). GER secondary to cow's milk protein allergy (CMA) and/or other food allergies (FA) may constitute a specific clinical manifestation of food hypersensitivity, such as CMA intolerance or FA (9-13).

During the diagnostic procedure not only the quality (the nature of the symptoms), but also the intensity of the course of GERD should be defined and assessed.

The basis for a diagnosis of GERD in children, regardless of age, is constituted by: a detailed history of the patient, establishing the cause of reflux symptoms, including the role of food hypersensitivity, and an evaluation of the clinical manifestations (typical or atypical).

24-hour esophageal pH probe monitoring is used as a diagnostic test to establish acid GER. However its results must always be interpreted together with the clinical manifestations of GER, other laboratory tests and additional test results of the upper gastrointestinal tract i.e. endoscopy or manometry for the child examined (14-18). In order to differentiate primary GER from GER secondary to CMA/FA, our department has introduced its own diagnostic and therapeutic algorithm. This algorithm includes the results of immunoallergologic tests and an oral food challenge test with a potentially noxious nutrient (10-13,19,20). 24-hour esophageal pH probe monitoring remains the most useful means for diagnosing atypical forms of primary or secondary GER (4,8,21-26).

Although a number of authors have contested this view, it would appear that 24-hour esophageal pH probe monitoring remains the method of choice for patients of Delayed developmental age with vexing typical symptoms, and especially in those that are not responsive to treatment (3,15,27-29).

The objective of the study was formulated as follows: to analyze any interdependence between the intensity of symptoms and the acid GER index in children diagnosed with primary GER and GER secondary to CMA/FA.

MATERIALS AND METHODS

A total of 138 children of various ages with symptoms of GER disease were included in the study.

The diagnostic procedure consisted of 24-hour esophageal pH monitoring with a 2-channel probe (distal and proximal leads). The following pH monitoring parameters were analyzed:

- the number of episodes of acid GER (a decrease of intraesophageal pH to below 4.0),
- the number of episodes of acid GER lasting more than 5 minutes (so-called „long episodes”), and
- the reflux index which measures the percentage of time that the pH is below 4.0 within the 24-hour period of intraesophageal pH monitoring.

The diagnostic procedure for determining pathological acid GER included implementation of ESPGAN and other authors' diagnostic criteria (15,30-32).

The borderline values in the quantitative and qualitative assessment of pathological GER in older children (above 3 years of age) in both leads were: the total number of acid GER episodes ($\text{pH} < 4.0/24\text{h}$) = 50, the number of acid GER episodes lasting more than 5 minutes ≤ 2 , percentage of time with pH below 4.0 (%) - total acid reflux index = 5.0%, percentage of time with pH below 4.0 (%) - supine acid GER index = 2.5%.

The esophageal pH monitoring results in the youngest children were juxtaposed alongside the borderline values compiled by Vandenplas et al. (14,33).

Information on the previous course of the disease (collected from parents or tutors) was at the same time compared with the type and intensity of the clinical symptoms of GER, with the help of our own scoring system (1-5 points)

- symptoms occurring episodically (lasting up to 6 weeks) of mild intensity - 1
- chronic symptoms (lasting over 6 weeks) of mild intensity, periodically treated with diet and/or acid suppressants - 2
- chronic symptoms of considerable intensity, requiring short-term pharmacological intervention - 3
- chronic symptoms of considerable intensity, requiring permanent diet and pharmacological ambulant treatment - 4
- chronic symptoms of very high intensity (requiring hospitalization) - 5

The primary check-up included a detailed physical examination of every patient. General condition and competence of systems, especially systems and organs at risk of the effects of GER (e.g. digestive system, respiratory system, cardiovascular system, nervous system), were assessed. In older children (over 3 years of age) with cow's milk allergy or other FA and GER, the constitutional features of allergy, according to Marks(34) were also taken into account.

In order to differentiate between primary (idiopathic) GER and GER secondary to CMA/FA, a study group of 138 children with GER was examined with the help of a diagnostic and therapeutic algorithm, including an oral food challenge test with a potentially noxious nutrient. An open-label food challenge study with cow's milk and/or other noxious nutrient (nutrient determined through anamnesis) was conducted in the youngest children (under 3 years of age) whereas a double-blind trial with placebo was carried out with older children (13,19,20).

The study was approved by the local Bioethical Committee of the Medical University of Białystok, Poland and informed parental consent was obtained from parents of the examined children.

Statistical analysis: For the purposes of statistical analysis, the variables under consideration were presented in the form of mean values and standard deviations. Since the distributions of the parameters examined were consistent with a normal

Table 1. Types of symptoms in 138 children with pathological GER diagnosed, according to the frequency of occurrence.

	Types of symptoms	Children with specified symptom	
		N = 138	%
1.	Bronchitis	35	25.4
2.	Vomiting	34	24.6
3.	Pneumonia	31	22.5
4.	Irritability / Crying	23	16.7
5.	Appetite loss / Food refusal	21	15.2
6.	Neurological symptoms	21	15.2
7.	Regurgitation	20	14.5
8.	Rumination	19	13.8
9.	Abdominal pains	17	12.3
10.	Failure to thrive	16	11.6
11.	Obstructive bronchitis	14	10.1
12.	Chronic cough	13	9.4
13.	Heartburn	11	7.9
14.	Belching / hiccups	9	6.5
15.	Coexistence of vesicoureteral reflux	9	6.5
16.	Wheezing / dyspnoea / paroxysmal cough	8	5.8
17.	Stiff neck (torticollis)	8	5.8
18.	Anaemia	6	4.3
19.	Foetor ex ore (bad breath)	5	3.6
20.	Spastic bronchitis	4	2.9
21.	Dysphagia (swallowing difficulty)	2	1.4
22.	Apnoeic attacks	1	0.7

distribution as assessed with the Kolmogorov compatibility test, variations analysis with a post-hoc Tukey test was used to compare the degree of intensity of the symptoms and the acid GER index: total and supine (proximal and distal leads). The significance level was $p < 0.05$. The calculations were carried out with the help of the statistical package SPSS ver.11.0.

RESULTS

24-hour intraesophageal pH monitoring with a 2-channel probe (distal and proximal leads) confirmed GER in all 138 patients. For diagnostic and therapeutic purposes, in view of the contribution of FA as a potential provoking or aggravating factor intensifying GER, all children underwent an oral food challenge test in order to determine the allergic cause of GER (13,19,20).

Primary GER was diagnosed in 76 (55.1%) of the children (group 1) examined. The mean age of these children was $x = 25.20$ months ± 27.28 .

The existence of pathological GER, secondary to CMA/FA was confirmed on the basis of an oral food challenge test giving positive results in 62 (44.9%) of the children (group 2). The mean age of these patients was $x = 21.53$ months ± 17.79 . The most important pH monitoring parameter, measured in the

children from both groups (1 and 2), was the acid GER index: total and supine - in distal and proximal leads.

The general characteristics of symptoms (typical and atypical) and their prevalence in both study groups are presented in *Tab. 1*. The clinical assessment of the intensity of symptoms and their comparative analysis against the acid GER index at the time of diagnosis is presented in *Tab. 2* and *Fig. 1,2*.

In study group 1, among the 76 children examined with primary GER, 31 patients (40.8%) were classified as degree 3, 33 patients (43.4%) – as degree 4 and 12 patients (15.8%) – as degree 5 of intensity of symptoms. In study group 2, among the 62 children examined with GER secondary to CMA/or other FA, 25 patients (40.3%) were classified as degree 3, 27 patients (43.6%) – as degree 4 and 10 patients (16.1%) – as degree 5 of intensity of symptoms.

In both study groups, patients with primary GER and GER secondary to CMA/FA, the degree of intensity of the symptoms was similar and appeared with comparable frequency. It appeared to be the case that, the higher the intensity of symptoms, the higher the acid GER index: total and supine, in both leads and in both groups examined.

Only in children with reflux symptoms with degrees of intensity of 4 and 5 (primary GER, group 1), did the values of the acid GER index in supine position, reveal a statistically

Table 2. Comparative analysis of the degrees of intensity of clinical manifestation against acid GER index: total and supine position (distal and proximal leads) in 76 children with primary GER (group 1) and in 62 children with GER secondary to cow’s milk allergy/ other food allergy (group 2).

Children examined.			PH-metric parameter (mean value, standard deviation)				Statistical significance (P)
Group	Symptom intensity	Number/ %	Distal lead		Proximal lead		
			Total GER index	Supine GER index	Total GER index	Supine GER index	
Group 1 (GER)	3	31/ 40.8	12.9 ± 4.7	5.4 ± 1.6	10.8 ± 4.6	4.9 ± 1.6	*P = 0,034 **P=0,051
	4	33/ 43.4	12.8 ± 6.2	6.8 ± 2.9*	10.8 ± 3.9	6.3 ± 2.8**	
	5	12/ 15.8	13.8 ± 4,9	7.7 ± 2.5*	11.8 ± 3.9	7.0 ± 2.5**	
	Total	76/ 100.0	13.4 ± 5.5	6.9 ± 2.6	11.2 ± 4.2	6.4 ± 2.6	
Group 2 (GER +CMA/FA)	3	25/ 40.3	16.2 ± 6.4	7.3 ± 3.2	9.7 ± 3.3	6.8 ± 2.9	P = ns
	4	27/ 43.6	16.9 ± 7.4	7.8 ± 2.7	10.8 ± 4.1	7.3 ± 2.7	
	5	10/ 16.1	19.9 ± 7.0	8.1 ± 2.6	11.6 ± 3.8	7.6 ± 2.6	
	Total	62/ 100.0	17.2 ± 6.9	7.6 ± 2.8	10.4 ± 3.8	7.1 ± 2.8	

Figure 1. Comparative analysis of degree of intensity of clinical symptoms against acid GER index in supine position in 76 children with primary GER (group 1), (distal lead).

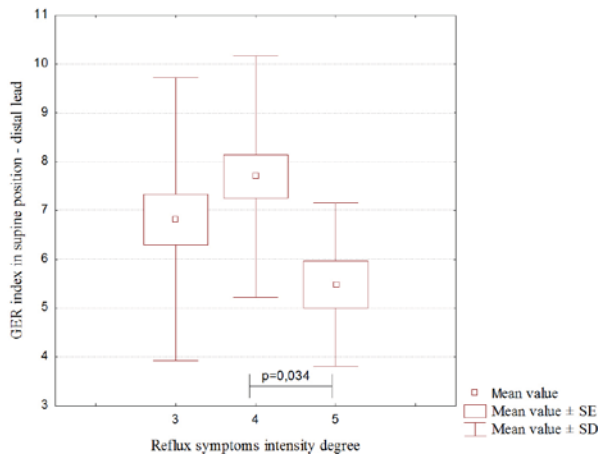
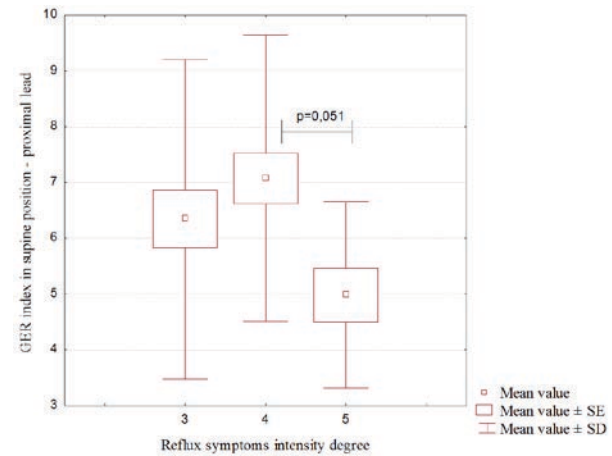


Figure 2. Comparative analysis of degree of intensity of clinical symptoms against acid GER index in supine position in 76 children with primary GER (group 1), (proximal lead).



significant diversity (p=0.034) in the distal lead, and borderline statistical significance (p=0.051) in the proximal lead (Tab. 2, Fig.1,2).

In study group 2, children with GER secondary to CMA/ or other FA, statistically significant differences between the intensity of symptoms and values of acid GER index: total and supine were not confirmed (p=ns) (Tab. 2).

DISCUSSION

Implementation of 24-hour pH monitoring enabled to confirm the existence of GERD in 138 children of various ages, admitted to our Department due to an escalation in clinical symptoms.

The algorithm administered in diagnostics and differentiation allowed us to define the cause of GERD and

assign the examined children to the following study groups : 76 (55.1%) children with primary GER (group 1) and 62 (44.9%) children with GER secondary to CMA/FA (group 2).

The children examined demonstrated a variety of clinical symptoms - typical or atypical, existing separately or in combination, and with a diverse frequency of appearance, as demonstrated in Tab. 1.

The results of our research are supported by the reports of authors from different clinical centers as well as our own, which suggest that GER in adolescents and adults may be responsible for the disruption of the anatomic and physiological functions of organs or systems, thereby giving rise to a variety of clinical manifestations. This diversity of clinical symptoms can be divided into two categories: typical and atypical symptoms (1,3,17,35-38).

Salvatore et al. carried out a clinical analysis of the clinical manifestations of GER, taking into account the age of patients.

Their results are in keeping with research conducted by other authors, including our own, with regard to similarities in the types of symptoms and their prevalence (5).

Given the increased accessibility of esophageal pH monitoring, its implementation is indicated in patients of different ages with various, typical and atypical, symptoms of chronic or recurrent character, suggesting GERD (14,27,39).

The ability to conduct 24-hour esophageal pH monitoring in conditions similar to those occurring naturally, allowing a child to maintain different activities throughout the day, allows us to make an objective assessment of the interdependence between the intensity of symptoms and the range of GER, expressed in the form of the GER index – total and supine, measured in both distal and proximal leads (4,22,26,31,32).

In both study groups of children with primary GER (group 1) and GER secondary to CMA/FA (group 2) participating in our research, in which an agreed scoring system for the intensity of symptoms was used, it was established that the higher the score for symptom intensity (ranging from 3 to 5), the higher the acid GER index: total and supine.

Given the fact, that the value of the acid GER index supine as measured (in both leads) should be regarded as an indication of the existence of reflux during night-time sleep, it may be inferred from the pathologic results of the test, that the type of symptoms registered is attributable to an extension of the damage to the mucosal membrane of the esophagus having been exposed to the long-lasting effects of acid gastric contents (4,22,26,31,32). In our study, this phenomenon appeared during the whole night with a comparable intensity of symptoms in patients from both groups, in the distal and proximal leads.

Our clinical observations were confirmed by the objective results of pH monitoring and therefore suggest that 24-hour esophageal pH monitoring with a 2-channel probe should constitute the preliminary examination in the diagnosis of acid GER, enabling the intraesophageal pH in both distal and proximal leads to be registered. At present the opinions of other authors on this particular subject remain diverse, which is partly consequent upon the increased costs of this test (15,22,28,32).

Age differentiation of our patients (infants and older children) and diverse pathological reasons for reflux (with determination of the primary or secondary background), intensity of symptoms and the extent of the course of disease, measured by scope (distal and proximal leads), and the character of symptoms (typical or atypical) had an influence on the results of the study conducted, taking into account both the clinical aspect and 24-hour gastroesophageal pH monitoring in 138 children with GERD.

The assumption during pH monitoring was that the higher the probe sensor is positioned in the esophagus, the smaller the number of reflux episodes that should occur, while the total time of gastroesophageal reflux (GER index) should be shortened by reason of more effective clearing and neutralization mechanisms of gastric contents in the esophagus.

The results obtained confirmed the validity of this procedure, as the mean values of the acid GER index were *significantly* reduced in the proximal part as compared to the distal part of the esophagus in patients from both study groups.

At the time of diagnosis of the disease, the percentage value of :

- total acid GER index – registered in the proximal part of the esophagus accounted for 84% and 61% of the value of the index registered in the distal part of the esophagus in group 1 and group 2, respectively
- in the supine position – the calculated percentage value of the acid GER index registered in the proximal part of the esophagus was comparable and constituted 92% and 93% of the values of the index registered in the distal part of the esophagus in group 1 and group 2, respectively.

It is to be supposed that high GER, reaching the proximal part of the esophagus may have a pathologic meaning in both study groups, especially in those with respiratory system symptoms (latent reflux, atypical symptoms), which suggests that microaspiration of gastric contents plays a causative role in the expression of clinical manifestations.

Our study demonstrates the validity of the use of a 2-channel probe in esophageal pH monitoring in children with symptoms from outside the gastrointestinal tract. The percentage value of high acid GER, registered in both study groups, was significantly higher than in other Polish centers (Krakow, Bydgoszcz) and accounted for 77.4% in the distal lead and 88.3% in the proximal lead. In these Polish pediatric centers, the GER was examined in a study group of children of up to 3 years of age, in whom there was a medical history of recurrent upper respiratory tract inflammation. pH monitoring with the use of a 1-channel probe confirmed the pathologic role of GER in 56% and 57% of children, respectively (40,41).

In another analyzed report, the diagnostic value, i.e. sensitivity, of 24-hour esophageal pH monitoring in diagnosing pathologic GER, was 89% in all patients diagnosed by this method and constituted 84% of all patients with atypical symptoms of GER (42).

The results of the acid GER index total and supine obtained, enrich our knowledge of the intensity of reflux during night-time sleep.

The pH value in the distal and proximal parts of the esophagus was comparable in both study groups which indicates the prospective pathogenetic role of this phenomenon in forming the clinical manifestations (night anxiety, night annoyance, change of position while asleep etc.) of the condition.

The results obtained for the acid GER index also have additional value. The similarity of the acid GER index for the two study groups, one with primary GER and the other with GER secondary to CMA/FA, at least in our study, does not differentiate between the two types and therefore does not serve as a determinant for allocating the children to the appropriate causative groups. It is therefore necessary to

perform immunoallergologic tests at a preliminary stage of the investigations.

In conclusion, the results of our study confirm that early complex diagnosis is vital in children with typical and atypical symptoms suggestive of GERD (and developing as primary GER or GER secondary to CMA/FA).

At the same time, the outcomes provide support for the opinions presented by other authors regarding the usefulness of 24-hour esophageal pH monitoring as an initial and reliable test in the diagnosis of acid GER, its monitoring, the intensity of the clinical manifestations, and modification of treatment (16,18,26,43).

CONCLUSIONS

In order to obtain an etiopathogenetic connection between existing primary GER or GER secondary to CMA/FA and its diverse clinical consequences in patients of various ages (infants, older children), 24-hour esophageal pH-monitoring with a 2-channel probe (distal and proximal leads) is recommended.

In this test, simultaneous registration of the pH of the distal and proximal parts of the esophagus, in comparison with standard 1-channel probe (distal lead) pH-monitoring, only in the distal esophagus, for both atypical and typical GERD, contributes more information towards the assessment of the course of the disease and selection of the appropriate conservative therapy.

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