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Manometric study of lower esophageal sphincter in children with primary acid gastroesophageal reflux and acid gastroesophageal reflux secondary to food allergy

Semeniuk J*, Kaczmarski M, Uścinowicz M

III Department of Pediatrics, Medical University of Bialystok, Poland

* CORRESPONDING AUTHOR:
III Department of Pediatrics
Medical University of Białystok,
Waszyngtona 17 Street
15-274 Białystok, Poland
fax: +48 85 742 3841
e-mail:Janexik@poczta.onet.pl (Janusz Semeniuk)

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ABSTRACT

Purpose: The comparison of values of selected lower esophageal sphincter (LES) manometric parameters measured in children suspected of gastroesophageal reflux disease (GERD) (preliminary study) and in children with primary acid GER and acid GER secondary to cow's milk allergy and/or other food (CMA/FA) in relation to the duration of the disease (prospective study).

Material and Methods: A 24-hour esophageal pH monitoring was performed on 264 children of both sexes suspected of GERD (mean age x = 20.78 ± 17.23 months). Pathological acid gastroesophageal reflux (GER) was diagnosed and divided into primary and secondary reflux in 138 children (52.3%). 76 patients (28.8%) (x = 25.2 ± 27.28 months) with primary GER made up Group 1. Group 2 consisted of 62 patients (23.5%) (x = 21.53 ± 17.79 months) with GER secondary to CMA/FA. 32 patients (12.1%) (x = 23.7 ± 12.63 months) with CMA/FA symptoms made up Group 3 (reference group). Prospective assessment of LES manometric parameters, i.e. resting LES pressure and LES length, was performed on 138 children with GER. Manometric parameters, resting LES pressure and LES length, measured at the preliminary study (0) and control studies (after 1, 2 and 8 years), were prospectively assessed in 138 children. The assessment resulted from clinical observation and/or conservative treatment.

Results: The mean value of resting LES pressure (mm Hg) before treatment was x = 11.75 ± 3.98 in Group 1, x = 11.05 ± 3.31 in Group 2, and x = 14.17 ± 3.86 in Group 3 (reference group). After 2 years of clinical observation, the mean value of resting LES pressure accounted for x = 13.71 ± 3.88 in Group 1, x = 13.01 ± 2.94 in Group 2, and x = 17.92 ± 3.36 in Group 3. The mean LES length (cm) before treatment accounted for x = 1.68 ± 0.72 in Group 1, x = 1.78 ± 0.70 in Group 2, and x = 2.0 ± 0.86 in Group 3. After 2 years of clinical observation, the mean LES length was x = 2.80 ± 0.40 in Group 1, x = 2.76 ± 0.40 in Group 2, and x = 2.97 ± 0.48 in Group 3. 12 children with persistent GERD (Group 1) and 8 children with persistent GERD and food allergy (Group 2) underwent manometric evaluation of LES after 8 years. No statistical differentiation of the mean values of resting LES pressure and LES length were shown in examined children of Groups 1 and 2 during prospective studies.

Conclusions: Manometric studies of LES assessing only resting LES pressure and its length in the examined children with acid GER do not clearly differentiate GER into primary and secondary refluxes to food allergy.

Key words: Esophageal manometry, lower esophageal sphincter (LES), gastroesophageal reflux (GER), children

INTRODUCTION

Gastroesophageal reflux (GER) is defined as an involuntary return of stomach contents back up into the oesophagus due to anatomical and functional defects of gastroesophageal junction, especially because of anomalies of the lower esophageal sphincter (LES) [1-3].

Commonly accepted division of reflux includes primary and secondary GER [1,3,4]. Primary GER could be physiological or pathological (with typical or atypical clinical manifestation).

Secondary GER is always pathological. Developmental anatomical anomalies of gastroesophageal junction, trachea, diaphragm or deformations of thorax have been regarded as

the main reasons of secondary GER. Nowadays, it seems that secondary GER could be attributable to allergic, neurological, systemic diseases, infections, genetic disorders, etc. [1-5].

Great progress in understanding pathogenesis of GER, especially primary GER, has been made recently. It is assumed that GER could be attributed to esophageal and gastric motility disorders due to the improper function of the nervous system and the muscular layer of the gastrointestinal tract [1,6-10].

Inefficient function of LES, i.e. constantly lowered resting LES pressure, and/or short-lasting, sudden and transient decrease in LES pressure, ineffective esophageal clearance, and disturbance in gastric voiding, trigger primary reflux [1,6-12].

At the same time, various studies suggest that cow's milk allergy and/or hypersensitivity towards noxious nutrients (CMA/FA) are triggering and aggravating factors of secondary GER in children of various age [13-19].

Cavatio et al. confirmed cow's milk allergy in 42% children diagnosed and treated because of GER symptoms [14]. Our studies also confirmed a cause-and-effect relationship between food allergy and GER in 43% of the youngest children [18].

The relationship between food allergy and GER in children above 1 year of age and older is still to be explained, because of the coexistence of GER with allergic diseases (inhalant allergy) in this age group [20,21].

Pathomechanism of acid GER secondary to FA still remains unclear. Therefore, the hypothesis suggesting that, in these patients, secondary, not primary, motility disorders of the upper gastrointestinal tract are the leading problem seems justified [22].

Implementation of manometric studies assessing sphincters' pressure and motor efficiency of this part of the gastrointestinal tract could enable better understanding of the pathogenesis of primary GER and GER secondary to CMA/FA [6-8,10,15,22].

Complex assessment is required in diagnostics of pathological GER and GER complications.

Quantitative assessment of the intensity of acid GER, the diagnosis of GERD and the confirmation of the relationship between reflux episodes and clinical manifestation is possible due to 24-hour pH-monitoring [23-31].

Manometric study enables the assessment of the motor efficiency of the oesophagus [6-8,11, 32,33]. In this study, LES pressure and LES length are both measured and LES localisation is determined. The attempt to differentiate GER into primary and secondary to CMA/FA can be made based on the results of manometry.

This study comprises the prospective analysis of selected manometric parameters of LES in children with diagnosed acid GER.

The aims of the study are the following:

- The comparison of measured LES manometric values in children suspected of gastroesophageal reflux disease (GERD) (preliminary study);
- The comparison of obtained values of selected LES manometric parameters in children with primary acid GER and acid GER secondary to cow's milk allergy and/or other food (CMA/FA) in relation to the duration of the disease (prospective study).

MATERIAL AND METHODS

Within a 3-year period, i.e. between 1992-1995, 7853 children were hospitalised in the III Department of Paediatrics, Medical University of Białystok (*Fig. 1*).

Among them, 735 (9.4%) children were selected with varied mono- and poly-organ symptoms suggesting gastroesophageal reflux disease (GERD), and they underwent diagnostic procedures and examinations including 24 hour pH-monitoring [23-31]. 264 of 735 children suspected of GERD had various diseases of gastrointestinal tract in their family history. 264 children suspected of GERD of both sexes (140- 53.0% boys and 124-47.0% girls) underwent 24-hour pH-monitoring [23-31]. The ages of the examined children were 1.5-102 months, and the mean age was $x = 20.78 \pm 17.23$ months.

The main criteria for including 264 children for further clinical studies were the following:

1. Gastrointestinal tract diseases present in the family (obtained through medical history taking),
2. The results of oesophagus pH-metric examinations, and
3. The results of endoscopic examinations of the upper part of the gastrointestinal tract.

A. Assignment of children into study groups

Having considered the results of 24-hour esophageal pH-monitoring, complex differential diagnostics, including eliminatory test of noxious nutrient, oral food challenge test [14,15,34,35,36] and analysis of nutrition, 264 children have been assigned into particular study groups (*Tab. 1*).

32 infants (12.1%) with physiological acid GER have been selected; 17 boys (6.4%) and 15 girls (5.7%), 1.5-4 months of age (mean age $x = 2.2 \pm 0.48$ months). The diagnosis was put forward based on the number of reflux episodes in pH monitoring only. The acceptable number of short lasting GER episodes was 30. The results of pH-monitoring parameters were within the reference values (age-specific reference values) [26].

As reflux symptoms in the youngest children were not complicated, they were considered physiological for this age group. These infants were not the subjects of further clinical analysis.

Pathological acid GER was diagnosed and divided into primary and secondary in 138 children (52.3%). These children were qualified into study groups: 1 and 2.

Primary acid GER was defined by reflux symptoms confirmed with anomalous results of esophageal pH monitoring, effective anti-reflux treatment, and the exclusion of other possible causes of the reported symptoms.

Figure 1. **Qualification of hospitalized children with symptoms suggesting gastroesophageal reflux disease (GERD). Diagnostic examinations confirming or excluding gastroesophageal reflux (GER).**

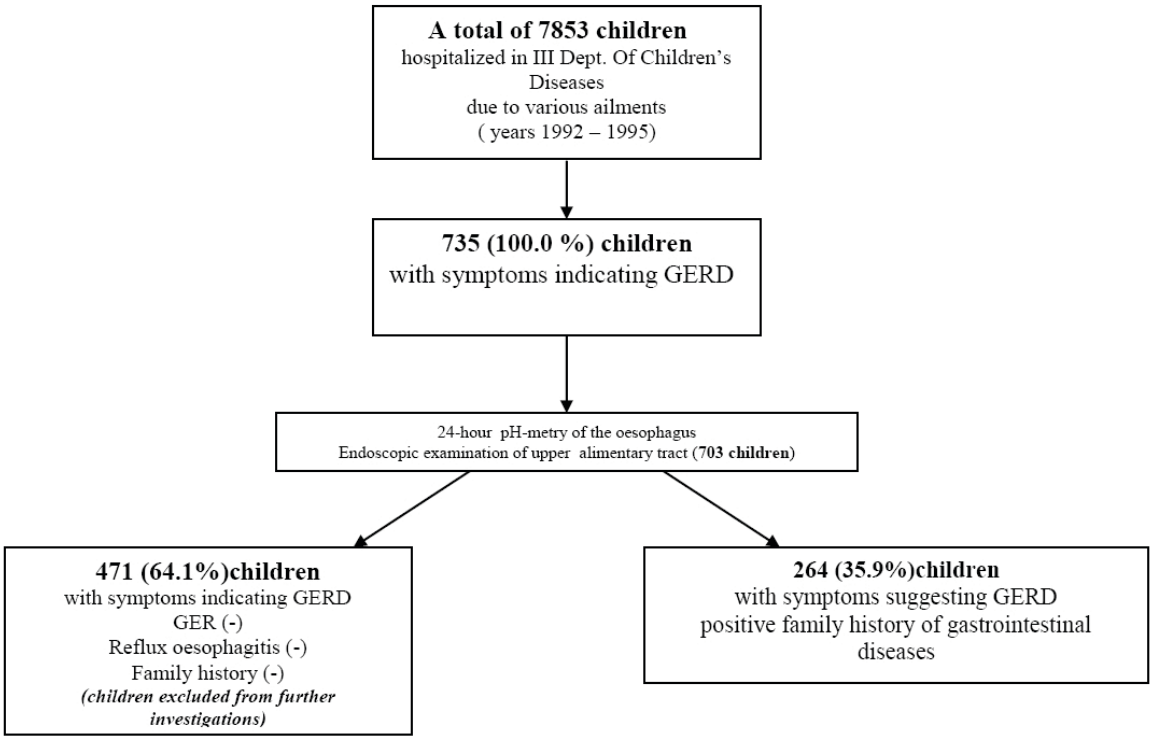


Table 1. **Qualification of 264 children suspected of GERD into study groups (at diagnosis).**

Groups of examined children	Examined children with reflux symptoms								
	Sex	Number		Age range					
				>1.5 - 4 months		>4 – 16 months		>16 – 102 months	
		N	[%]	N	[%]	N	[%]	N	[%]
Infants with *physiological acid GER** N=32	*Boys*	*17*	*6.4*	*17*	*6.4*	-	-	-	-
	Girls	*15*	*5.7*	*15*	*5.7*	-	-	-	-
Group 1 primary acid GER N=76	Boys	39	14.8	-	-	23	8.7	16	6.1
	Girls	37	14.0	-	-	21	7.9	16	6.1
Group 2 acid GER secondary to CMA/ FA N= 62	Boys	33	12.5	-	-	16	6.1	17	6.4
	Girls	29	11.0	-	-	14	5.3	15	5.7
Group 3- reference group CMA/ FA N= 32	Boys	19	7.2	-	-	7	2.6	12	4.5
	Girls	13	4.9	-	-	5	1.9	8	3.0
Children without GER (-) and CMA/ FA (-)* N= 62	Boys	32	12.1	-	-	8	3.0	24	9.1
	Girls	30	11.4	-	-	10	3.8	20	7.6
Total		264	100.0	32	12.1	104	39.4	128	48.5

*children not included in further clinical analysis

Group 1 included 76 patients (28.8%) of both sexes (39 boys-14.8%, 37 girls-14%), 4-102 months of age (mean age x = 25.2 ± 27.28 months) with primary GER.

Acid GER secondary to CMA/FA was defined by reflux symptoms confirmed with anomalous results of esophageal pH-monitoring and effective anti-allergic treatment (eliminatory diet, anti-allergic drugs) or combined treatment (anti-allergic and anti-reflux) with the exclusion of other than allergy possible causes of the reported symptoms. Other allergy symptoms, the family history of allergy and a positive result of oral food challenge test with milk or another noxious nutrients were also taken into consideration.

Group 2 consisted of 62 children (23.5%) of both sexes (33 boys-12.5%, 29 girls-11.0%), 4-74 months of age (mean age x = 21.53 ± 17.79 months) with GER secondary to CMA/ FA.

Acid GER was not confirmed in 94 patients (35.6%) out of 264 children with symptoms suggesting GER. 32 children (12.1%) of both sexes (19 boys-7.2%, 13 girls-4.9%), 7-69 months of age (mean age x = 23.7 ± 12.63 months) with symptoms of CMA/FA were selected from this group and constituted Group 3 – reference group.

Neither a reflux nor allergic cause of existing symptoms was confirmed in the remaining 62 patients (23.5%), (32 boys-12.1%, 30 girls-11.4%), 4-102 months of age (mean age x = 31.3 ± 27.98 months). These children were not the subjects of either preliminary analysis or further analysis that could stem from prospective clinical observation.

B. Manometric study of LES

Out of 264 children suspected of GERD, 170 patients (64.4%) underwent manometric study of LES in order to determine its localisation and changes in resting pressure and length [6-8,11,32,33]. Preliminary study (0) was performed at diagnosis and the qualification of patients into study Groups 1, 2 and 3 before conservative treatment.

Prospective assessments of LES manometric parameters measured at the preliminary study and control studies, which stemmed from clinical observation and/or conservative treatment, were conducted on 138 children with GERD.

Manometric parameters of LES were defined as follows:

* In 76 children with primary GER (Group 1) – before treatment (preliminary study - 0) and after 1 year of treatment; in 46 children – after 2 years and in 12 children – after 8 years of clinical observation and/or dietary and pharmacological treatment, and

* In 62 children with secondary GER (Group 2) – before treatment (preliminary study - 0) and after 1 year treatment, in 47 children – after 2 years, and in 8 children – after 8 years of clinical observation and/or only anti-allergic treatment or anti-allergic +anti-reflux treatment.

On the 32 children with CMA/FA (Group 3 - reference group), preliminary manometric studies of LES (0) and a control study were conducted – only after 2 years of clinical observation and/or conservative treatment.

The comparative assessments of LES motor activity between and within the study groups: 1, 2 and 3, after 2 years of clinical observation and/or conservative treatment were performed on the basis of selected manometric parameters, i.e. resting LES pressure and LES length.

The study of LES motor activity was performed according to the standard methodology described in the literature, with a 4-channel catheter placed into oesophagus through the nasal duct and stationary flow system Polygraph by Synectics Medtronic. The study was recorded by a computer and was analysed with "Polygram" software by Synectics Medtronic, considering manometric protocol in force [6-8,11,32,33]. In the youngest children, short-lasting anaesthetic was used in order to provide full comfort to the examined child.

The following selected parameters of LES were taken into consideration in the analysis of manometric recording:

- **Resting LES pressure** (stadion pull through SPT) / mmHg – pressure assessed during catheter movement -1cm upwards, with 10-second-pause, calculated as a mean of measurements in 4 channels [6].

Normal mean value:

x = 24.20 ± 10.10 in healthy adults (n= 20), according to Castell [37] and

x = 12.98 ± 4.43 in children without GERD (n= 16; mean age x = 11.11 ± 3.25), according to Fyderek [6];

- **LES length,** i.e. proper sphincter (cm) – size of high pressure zone (HPZ), where pressure was 50% higher than maximum pressure.

Normal mean value:

x = 4.10 ± 0.90 in healthy adults (n= 20), according to Thor [8] and

x = 2.85 ± 0.54 in children without GERD (n= 16; mean age x = 11.11 ± 3.25), according to Fyderek [6].

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

Statistical Analysis

The statistical analysis of the results comprised arithmetical mean, standard deviation, minimal and maximal values and median – for measurable features and quantitative percentage distribution for qualitative features.

To compare the groups, features compatible with normal distribution, assessed with Kolomogorov compatibility test, were assessed together with the post hoc Bonferroni one-way analysis of variance. Features non-compatible with the distribution underwent Kruskal-Wallis test and, if the differences were statistically significant, Mann-Whitney test was applied. Statistical significance was $p<0.05$. Calculations were performed with the help of statistical package SPSS'12.0 PL.

RESULTS

170 children, 4-102 months of age suspected of GER underwent manometry including resting LES pressure (mmHg) and LES length (cm) in order to assess the motor function of LES.

The analysis of age of children from particular groups did not show statistically significant differentiation of mean values between the groups ($p>0.05$). These parameters were evaluated in consecutive manometric examinations: preliminary examination (0) at diagnosis and control examinations during clinical observation and periodic conservative treatment (prospective study).

Analyses of mean values of manometric LES parameters were conducted on 170 children all together, including 138 children with pathological acid GER: primary (Group 1), secondary to CMA/FA (Group 2) and in 32 children with CMA/FA (Group 3 – reference group).

Resting LES pressure (mmHg) (Table 2, Fig.2)

In children with primary GER (Group 1), mean values of resting pressure before treatment x = 11.75 ± 3.98 were comparable

Table 2. **Comparison of selected manometric parameters of LES in children with primary and secondary acid GER and in children with CMA/FA (prospective study).**

STUDY GROUPS	**Manometric parameters of lower esophageal sphincter** Range of values ; mean value; standard deviation (± SD); median; p							
	Resting LES pressure(mmHg)				**LES length** (cm)			
	Before treatment (0)	Clinical observation and/or treatment in progress			Before treatment (0)	Clinical observation and/or treatment in progress		
		After 1 year	After 2 years	After 8 years		After 1 year	After 2 years	After 8 years
Group 1 primary GER (N=76)	5.50 – 21.10 11.75 ± 3.98 (10.80)	8.10 – 24.40 14.86 ± 4.83 (13.20)	7.70 – 23.10 13.71 ± 3.88 (12.75)	17.80-25.30 21.56 ± 2.75	0.76 – 3.25 1.68 ± 0.72 (1.49)	1.56 – 3.25 2.13 ± 0.51 (1.90)	2.32 – 3.75 2.80 ± 0.40 (2.67)	2.75-3.82 3.39 ± 0.31
Statistical differentiation within the groups (p)	0–1, p=0.0001; 0 – 2 , p=0.0001; 0 - 8, p=0.0022; 1 – 2, p=0.0012; 1 – 8, p=0.0022; 2 – 8, p=0.0047				0 – 1, p=0.0001; 0 – 2, p=0.0001; 0 - 8, p=0.0037; 1 – 2, p=0.0001; 1 - 8, p=0.0022; 2 – 8, p=0.0022			
Group 2 GER secondary to CMA/FA (N=62)	5.20 – 19.30 11.05 ± 3.31 (11.05)	7.20 – 19.70 13.56 ± 4.01 (13.90)	8.10 – 20.80 13.01 ± 2.94 (12.80)	16.60-20.20 18.84 ± 1.21	0.73 – 3.44 1.78 ± 0.70 (1.60)	1.58 – 3.40 2.07 ± 0.53 (1.79)	2.12 – 3.80 2.76 ± 0.40 (2.58)	2.53-3.74 3.30 ± 0.39
Statistical differentiation within the groups (p)	0 – 1, p=0.0001; 0 – 2, p=0.0001; 0 - 8, p=0.0117; 1 – 2, ns; 1 – 8, p=0.0117; 2 – 8, p=0.0180				0 – 1, p=0.006; 0 – 2, p=0.0001; 0 - 8, p=0.0357; 1 – 2, p=0.0001; 1 - 8, p=0.0117; 2 – 8, p=0.0117			
Group 3- reference group CMA/FA (N=32)	8.80 – 21.70 14.17 ± 3.86 (13.10)	-	13.20 – 24.70 17.92 ± 3.36 (16.75)		0.83 – 3.43 2.00 ± 0.86 (1.69)	-	2.18 – 3.78 2.97 ± 0.48 (2.86)	
Statistical differentiation within the groups (p)	0 – 2, p=0.0001				0 – 2, p=0.0001			

Figure 2. **Statistical differentiation of mean values of resting LES pressure between the Groups 1,2 and 3 (prospective study: preliminary (0) and control study after 1 and 2 years) .**

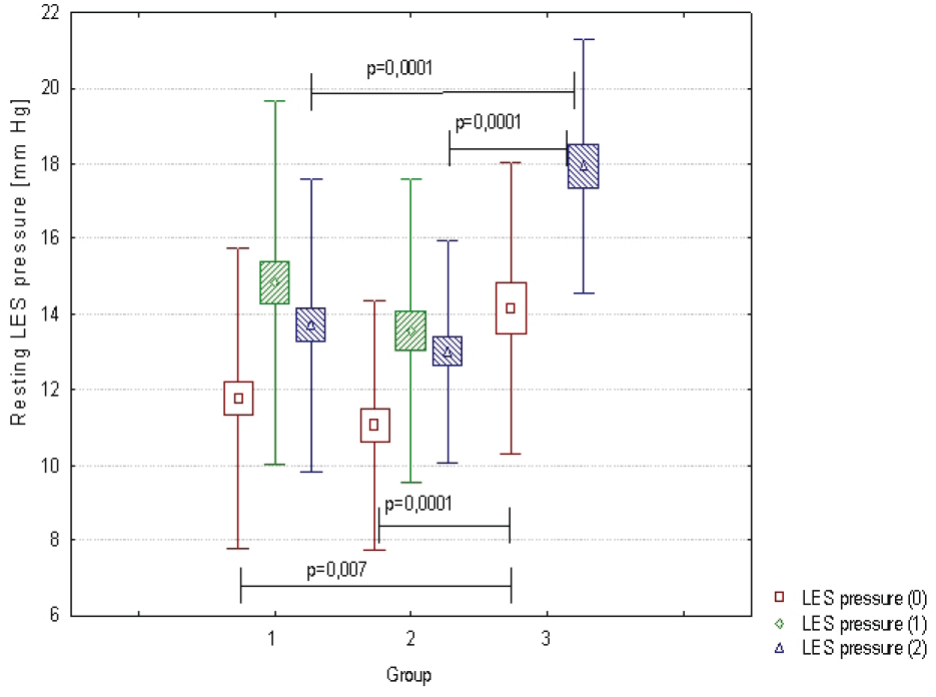
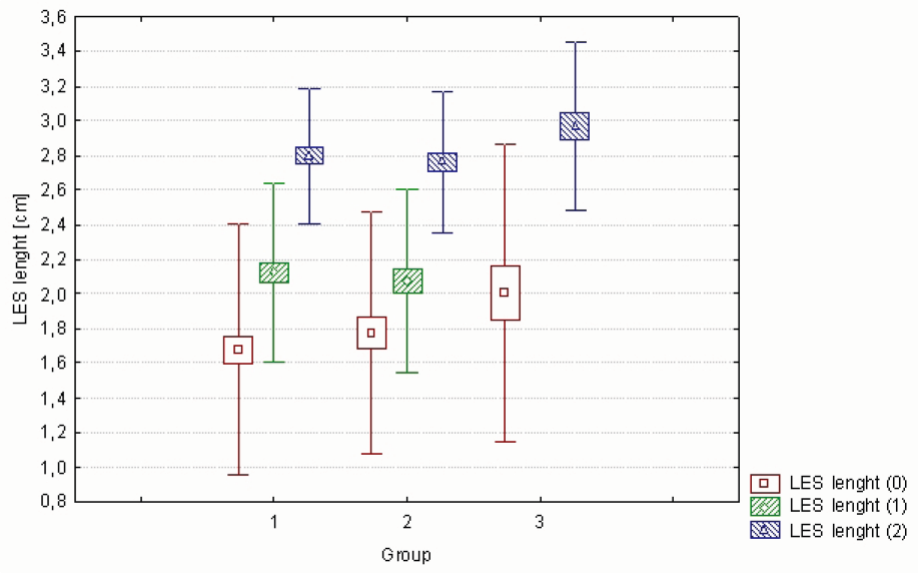


Figure 3. **Statistical differentiation of mean values of LES length between the Groups 1,2,3 (prospective study: preliminary (0) and control study after 1 and 2 years).**



to values in children with GER secondary to CMA/FA (Group 2) x = 11.05 ± 3.31 and were lower than resting pressures in children from Group 3 –reference group (x = 14.17 ± 3.86).

Mean values in Group 1 were increasing with time of clinical observation and treatment and accounted for x = 14.86 ± 4.83 and 13.71 ± 3.88 after 1 and 2 years of clinical observation, respectively.

Children with GER secondary to CMA/FA (Group 2) had the lowest value of resting pressure before treatment, x = 11.05 ± 3.31 in comparison with mean values obtained in Group 1 (x = 11.75 ± 3.98) and 3 (x = 14.17 ± 3.86). The mean values in Group 2 accounted for x = 13.56 ± 4.01 after 1 year and 13.01 ± 2.94 after 2 years of treatment.

Children with CMA/FA (Group 3 –reference group) had the highest values of mean resting pressure before treatment, x = 14.17 ± 3.86 in comparison with mean values in study Groups 1 and 2.

After 2 years of clinical observation and/or administered treatment on Group 3, mean values accounted for x = 17.92 ± 3.36. That was the only control study in this group. The differentiation within the group comprised the preliminary study (0) and study after 2 years of treatment and was statistically significant ($p<0.05$).

Mean values of resting LES pressure in Groups 1, 2 and 3 showed statistically significant differentiation within the groups ($p<0.05$), between the preliminary study (0) and control studies. Statistical significance was higher in Group 1 than in Group 2, only between 1st and 2nd year of clinical observation and treatment; after the 2nd year it was comparable in particular groups.

Statistically significant differentiation of the mean values of resting LES pressure between the study groups ($p<0.05$) (normal distribution) was shown during the preliminary study, during clinical observation and treatment.

Statistical significance was confirmed between Groups 1 and 3, 2 and 3 before and after 2 years of treatment; whereas, no statistical significance was shown between Groups 1 and 2 during the study.

LES length (cm) (*Tab. 2, Fig. 3*)

Children with primary GER (Group 1) had the lowest mean LES length (measured before treatment) x = 1.68 ± 0.72 in comparison with mean values obtained in remaining groups: Group 2 (x = 1.78 ± 0.70) and Group 3 (x = 2.0 ± 0.86).

During clinical observation and/or treatment in Group 1, mean values increased and accounted for x = 2.13 ± 0.51 after 1 year and 2.80 ± 0.40 after 2 years.

Children with GER secondary to CMA/FA (Group 2) had mean length measured before treatment that accounted for x = 1.78 ± 0.70. This value was similar to mean values in children from Group 1, x = 1.68 ± 0.72, and was lower than LES length in children from Group 3, x = 2.0 ± 0.86. During clinical observation and/or treatment in Group 2, mean values were higher, x = 2.07 ± 0.53 after 1 year and x = 2.76 ± 0.40 after 2 years.

Children with CMA/FA (Group 3) had the highest mean values of length (measurement before treatment) x = 2.0 ± 0.86 in comparison with the mean values obtained in Groups 1 and 2. After 2 years of clinical observation and/or treatment in Group 3, mean values increased, x = 2.97 ± 0.48 (control study only).

Differentiation of mean values of LES length measured in Groups 1, 2 and 3 were statistically significant within the groups ($p<0.05$) between the preliminary study (0) and control studies.

Statistical significance was comparable in particular groups. During the preliminary study, clinical observation and treatment, there was no statistically significant differentiation of mean values of LES length between the study groups.

In 12 patients with persistent primary GER (Group 1) and in 8 patients with persistent GER secondary to CMA/FA (Group 2), chronic GERD was subjected to longer observation (over 2 years) than in remaining patients from both study Groups 1 and 2. These patients had control manometry of LES after 8 years of clinical observation and/or periodic conservative treatment.

The reason for the remote in time comparative manometric analysis of LES (follow up) in these patients was a significant improvement of clinical presentation and the results of control pH monitoring performed at the same time.

During the studies, 12 patients from Group 1 were of mean age x= 203.83 ± 7.85 months (17 years) higher than the mean age of 8 patients from Group 2, x= 173.25 ± 9.71 months (14 years). Statistically significant age differentiation ($p<0.05$) was shown between the groups.

These patients were selected and underwent remote assessment of motor function of LES, during the disease, by measurement of manometric parameters, such as resting pressure and LES length. Mean values of measured LES parameters at that time are presented in *Tab. 2*.

*** Resting LES pressure** (mmHg)

In 12 children with persistent primary GER (Group 1) the mean value of resting LES pressure accounted for x = 21.56 ± 2.75 and was higher than the mean value of pressure in 8 children with persistent GER secondary to CMA/FA (Group 2), x = 18.84 ± 1.21.

Differentiation of mean values of resting LES pressure in selected patients from Groups 1 and 2 was statistically significant ($p<0.05$) within the groups, between the preliminary study (0) and control studies. Statistical significance was higher in Group 1 than in Group 2 during the prospective study. At the same time, differentiation of mean values of resting LES pressure between the groups in patients selected from group 1 and 2 after 8 years of studies is on the verge of statistical significance ($p=0.0586$).

*** LES Length** (cm)

The mean value of LES length was x = 3.39 ± 0.31 in 12 children with persistent primary GER (Group 1), and it was higher than mean value of LES length in 8 children with persistent GER secondary to CMA/FA (Group 2), x = 3.30 ± 0.39.

Differentiation of mean values of LES lengths in selected patients from Groups 1 and 2 was statistically significant ($p<0.05$) within the groups, between the preliminary study (0) and control studies. The only exception was differentiation of values in children from Group 2, after 1 year of treatment, which was on the verge of statistical significance.

There was no statistically significant differentiation of mean values of LES length between the groups in selected patients from both Groups 1 and 2 after 8 years of studies.

DISCUSSION

Pathophysiological background of GERD, regardless of the cause of disease (primary or secondary), includes the following: the mechanic inefficiency of lower esophageal sphincter (LES), motility disorders of the esophageal body, impairment of gastric voiding: therefore, leads to the impairment of esophageal clearance, an extension of time that the mucous membrane is exposed to hydrochloric acid, and the progress of the disease with complications such as reflux-induced esophageal inflammation [1,6-12].

The efficiency of anti-reflux mechanism in patients with primary GER and GER secondary to CMA/FA still remains unclear [1,6-10,13-19].

Transient and spontaneous relaxation of LES is considered to be a very important pathogenic factor of primary GER [1,6-10]. It seems that, in patients with GER and allergy, this factor does not play the most important role in the pathogenesis of the disease. There is no direct data explaining the mechanisms leading to reflux in patients with food allergy in the quoted literature [13-19,22].

Presumably, secondary motility disorders, for example gastroesophageal junction with constantly persistent inefficiency of LES, result from chronic allergization of the upper gastrointestinal tract with noxious nutrient [13-19,22].

Ravelli et al. reported that provocation with cow's milk in infants allergic to milk proteins led to bradygastry and late gastric voiding [38]. Late gastric voiding triggers the extension of stomach's wall muscles and leads to activation of afferent fibers of vagus nerve and hyper-relaxation of LES [38]. In Poland, Kaczmarski et al. made similar observations suggesting food hypersensitivity being the cause of GER [18,22]. To confirm the harmful role of food (cow's milk proteins, soy milk proteins, citrus fruit and other food), they indicated pathogenic effects in the mucous membrane of the oesophagus and stomach (hyperaemia, swelling, erosions) causing abdominal pains. These changes are strictly connected with the relaxation of LES (low pH and possible phase graphic recording), which allows the influence of allergic factor on respiratory tract (obstructive or spastic bronchitis) [18,22]. Therefore, complex assessment of LES efficiency is vital in determining the role of its primary or secondary impairment in triggering or aggravating various symptoms.

In our own studies, in order to assess motor activity of LES in children, the measurement of 2 main manometric parameters were performed, i.e. resting LES pressure (mmHg) and LES length (cm). Although data obtained from measurements is not utterly sufficient, it significantly contributes to the explanation of pathophysiology of reflux. 170 children suspected of GERD underwent preliminary manometry at diagnosis and qualification into study groups.

There was no statistical age differentiation ($p>0.05$) at that time between the groups, i.e. in children with primary and secondary acid GER and in children with allergy but without

acid GER, which underwent manometric study.

According to the literature regarding interdependence between the age and length of oesophagus, it seems that the length of oesophagus, and therefore LES length, elongate with age, including the intra-abdominal part of oesophagus, and influence anatomical development of proper His angle. It indirectly influences the increase of resting LES pressure and motor activity of LES [6,7,11].

The lack of reference values for manometric parameters assessed in the youngest children may stem from limited possibilities and greater technical difficulties in performing this type of functional study. It also results from greater anatomical and functional differentiation of this part of gastrointestinal tract in children at this age, during their ontogenetic development [6-8,10,37]. Manometric studies of LES performed in 1970's of the last century on 680 newborns and little infants (4000 measurements) by Boix-Ochoa et al. support the last mentioned cause [39]. Their results suggest that functional maturation of LES does not stay in a close relation either with date of birth of a child (prematurity) or with weight at birth (intrauterine fetal dystrophy). Maturation usually takes first 4-6 weeks after birth, and occasionally may last till 12-15 months [1,39].

During the neonatal period, the physiological value of LES is lower. According to Fyderek, it is from + 1.6 to + 6.2 mm Hg and in later period from + 15 to + 30 mm Hg [6,7].
It is widely accepted that resting LES pressure values are similar to values in adults between 6 months and 1 year of age [6].

Resting LES pressure value stem from its anatomical properties. It is defined as "physiological concept" by many authors, as it is composed of smooth muscles that have specific abilities to keep this resting pressure and contract or relax under various stimuli, e.g. enterohormonal, neurogenous, pharmacological and nutritive [1,6,10].

The length of LES, which is determined at manometric study after birth, is only 3 mm and gradually increases with the age. In infants under 3 months of age, it is 0.5-0.75 cm; whereas, in older infants it does not go beyond 1cm, which unfortunately does not protect proper function of antireflux barrier at this age. In children above 1 year of age, the length is between 1-3 cm, and in older children and adults, it is 3-5 cm [6,40,41].

The aforementioned interdependencies have been confirmed in our own studies.

Comparative assessment of motor efficiency of LES was performed on 138 children with GERD on the basis of primary and secondary acid GER, using mean values obtained from measurement of resting LES pressure and LES length in the preliminary study and control studies. For this reason, prospective clinical observation and periodic conservative treatment after 1, 2 and 8 years were conducted (Table 2; Fig.2 and 3). The analysis of mean values of both measured LES manometric parameters showed their gradual growth with time and statistically significant differentiation within the groups ($p<0.05$) between the preliminary study and control studies in both groups; in children with primary GER and in children with GER secondary to FA. The lack of differentiation between mean values of resting pressure in this group obtained in control studies, after 1 and 2 years, is worth mentioning. It may result from less rigorous eliminatory diet at that time, which is a vital part of the treatment of secondary GER.

Statistical significance of the obtained values of both LES parameters were comparable (almost identical) in children with primary and secondary GER. Mean values of resting LES pressure and LES length in children with primary and secondary acid GER were similar. However, they were lower than mean values of these parameters in children with cow's milk allergy and/or other food and without acid GER, but differences were not statistically significant ($p>0.05$).

Genetically conditioned proneness to GER, described by few authors recently (Hu, Orenstein), could have the possible influence on the aforementioned interdependencies [42,43].
Statistically significant differentiation of mean values of resting LES pressure were shown between groups 1 and 3, 2 and 3 in the preliminary study and control studies – after 2 years of clinical observation and/or treatment (Fig.2). There was no statistically significant difference between these values in children with primary and secondary GER at that time.
These statistical interdependencies support the hypothesis that lower resting LES pressure considerably promotes GER [1,6-12].

There was no statistically significant difference ($p>0.05$) between the groups in the case of LES length (Fig.3).

Final assessment of LES motor efficiency in the case of its anatomical and functional maturity was conducted after 8 years of prospective clinical observation, and periodic treatment was given to 12 patients with persistent GERD on the basis of primary GER and in 8 patients with persistent GERD due to GER secondary to persistent food allergy (Table 2). At that time in both study groups, mean values of both LES manometric parameters were the highest. Differentiation of resting pressure values between the groups in 12 patients from Group 1 and 8 patients from Group 2 was expressed the most faintly (on the verge of statistical significance; $p=0.0586$).

Like in previous studies, there were no statistically significant differences ($p>0.05$) between mean values of LES length assessed in patients from Group 1 and 2, nor pressure, i.e. after 8 years. It presumably stems from the proper ontogenetic development of the gastroesophageal junction.

Mean values of resting pressure and LES length obtained in our own studies in consecutive manometric measurements were lower before treatment; and, with the time of study, they were similar (or even higher) to values of the parameters determined in healthy children and defined as normal by Fyderek et al. in age group (6.1 – 16.7) [6]. In older children, the minimal reference values were resting LES pressure 10 mm Hg, LES length 2 cm.

Kwiecień et al. performed manometric assessment of LES function on 26 children aged 7-18 years (mean age 14,75 years) with chronic asthma [40]. Obtained results were as follows:

mean resting LES pressure x= 15.15 ± 8.93 mmHg, mean LES length x= 2.79± 1.15 cm. The results of the aforementioned measurements of both LES parameters were comparable with the results in healthy children, accepted as reference values for older children, published by Fyderek [6]. In the case of resting LES pressure, they were slightly higher than values in our own studies: preliminary (before treatment) and control (after 1 year and 2 years), but significantly lower ($p<0.05$) than values obtained after 8 years in both study groups. These values were comparable with the results obtained in the preliminary and control study, exclusively after 2 years in groups of children with food allergy but without GER.

In the case of LES length obtained by Kwiecień et al. [40], mean values were higher than the results obtained in our own studies, i.e. the preliminary study- in all groups, after 1 year - in Groups 1 and 2; comparable with results of control study after 2 years in all groups and significantly lower ($p<0.05$) than mean values obtained after 8 years – in Groups 1 and 2.

CONCLUSIONS

Manometric studies of LES assessing resting LES pressure and LES length in study children enable better understanding of pathogenic mechanisms of acid GER, but do not differentiate GER into primary and secondary to food allergy.

The results obtained in manometric study of LES in children with primary and secondary GER did not show statistically significant differentiation of mean values of both: resting LES pressure and LES length between the groups.

The results of our own prospective manometric studies of LES in children are consistent with the research and studies that concern children with primary GER. However, it is impossible to relate the results with the results obtained in our own studies with children with GER secondary to CMA/FA, due to lack of adequate data concerning the assessment of LES manometric parameters in this study group.

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