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Role of esophageal symptoms in the diagnosis of gastroesophageal reflux disease in children with recurrent and chronic respiratory diseases

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Abstract: ***Introduction:*** Gastroesophageal reflux disease (GERD) is one of comorbid diseases, that worsen the course and outcomes of respiratory pathology. The study aimed to determine role of esophageal symptoms in the diagnosis of GERD in children with recurrent and chronic respiratory diseases (RCRD). ***Methods:*** The study included 125 children (70 boys, 55 girls), median 3,75 years (interquartile range, IQR – 1,21-9,38 years), with RCRD, refractory to standard therapy. GERD was diagnosed on the basis of clinical and complex instrumental examination, including fluoroscopy esophagus with contrast, esophagogastroduodenoscopy (EGDS), 24-hour esophageal pH-monitoring, dual pH-multichannel intraluminal impedance (pH-MII). ***Results:*** In children with RCRD, the frequency of GERD was 86,4%. Among children without esophageal manifestations of GERD, pathological reflux was confirmed by instrumental methods in 81% of patients; in children with esophageal manifestations - 92%, with no statistically significant differences (p = 0,0637). Nonacid reflux is more common in patients without esophageal manifestations of GERD. ***Conclusions:*** The frequency of GERD in children with RCRD is very high. It is possible to screen GERD in children with RCRD, independent on the presence of clinical esophageal symptoms.

Keywords: GERD; respiratory diseases; diagnosis.

1. INTRODUCTION

Respiratory diseases occupy a leading place in the structure of morbidity and mortality in children around the world, especially in developing countries. There are comorbid diseases that worsen the course and outcomes of respiratory pathology. One of these diseases is gastroesophageal reflux disease (GERD) - a chronic recurrent disease characterized by esophageal and extraesophageal clinical manifestations and various morphological changes in the esophageal mucosa due to retrograde reflux of gastric or gastrointestinal contents into esophagus. The extraesophageal manifestations of GERD include a variety of cardiovascular, otorhinolaryngological (for example, recurrent otitis media), dental pathology, but the most numerous groups of diseases associated with extraesophageal manifestations of GERD are respiratory. Respiratory manifestations of GERD include chronic pharyngitis, chronic laryngitis, recurrent (spastic) croup, recurrent aspiration bronchitis, recurrent pneumonia, bronchiolitis obliterans, bronchiolitis obliterans with organizing pneumonia, bronchiectasis. In newborns and children in the first months of life, symptoms of GERD will be pathological regurgitation, low rates of weight gain, refusal to feed, dysphagia, chronic cough, and the development of apnea [1]. However, GERD often occurs without any esophageal symptoms, including in patients with respiratory diseases. Thus, in infants with wheezing, GERD was

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diagnosed in 60,5% of cases, while 60,9% of these patients did not have typical esophageal symptoms [2]. From 1/3 to 1/2 of patients with asthma and GERD do not have characteristic esophageal symptoms [3], in another study typical symptoms of GERD, such as heartburn, were present only in 16% of patients with extraesophageal manifestations of the disease [4, 5].

The symptoms of GERD are known to vary widely with the age of children and are nonspecific. Poor weight gain is an important symptom that requires clinical alertness. In infants, crying, irritability, sleep disturbances, intestinal cramps, and Sandifer syndrome are considered equivalents of heartburn [1].

Diagnosing GERD is challenging because there is no best test method. Esophagogastroduodenoscopy (EGDS) is the only diagnostic tool for identifying esophagitis, however, according to the results of the studies, erosive esophagitis was diagnosed in 15-71% of the examined patients [6]. It has been shown that dual pH-multichannel intraluminal impedance (pH-MII) is the most accurate method for diagnosing GERD, since it detects up to 96% of all refluxes, while isolated 24-hour pH-monitoring (24-pH) revealed only 76% of refluxes [7, 8].

The aim of the study was to determine role of esophageal symptoms in the diagnosis of gastroesophageal reflux disease in children with RCRD, refractory to standard therapy.

2. MATERIALS AND METHOD

2.1. Study population

All children with RCRD, hospitalized for a cause of poor response to respiratory-specific therapy, at the Department of Thoracic Surgery of the Morozovskaya Children's City Clinical Hospital, from November 2017 to September 2019 were enrolment for an uncontrolled cohort, prospective, single-center, comparative study.

Inclusion criteria included the presence of RCRD refractory to standard therapy: chronic pharyngitis, chronic laryngitis, recurrent otitis media, recurrent croup, bronchopulmonary dysplasia, recurrent pneumonia, recurrent bronchitis, recurrent obstructive bronchitis, bronchial asthma, obliterating bronchiolitis, bronchiolitis obliterans with organizing pneumonia, bronchiectasis; age from 3 months to 17 years.

Exclusion criteria included established diagnoses of cystic fibrosis, primary ciliary dyskinesia, foreign bodies of the respiratory tract, congenital malformations of the respiratory tract, pulmonary tuberculosis, primary immunodeficiency; lack of RCRD; age less than 3 months; the use of antireflux therapy during the study of 24-pH and pH-MII.

At the first stage of the study, all patients were divided into 2 groups based on the identification of esophageal manifestations of GERD based on the results of a questionnaire survey or identification of disease equivalents (depending on age). Group A consisted of 63 children with typical esophageal symptoms of GERD or their equivalents, group B - 62 children without this symptomatology. We compared main characteristics between 2 these groups, including age, sex, structure of RCRD, duration of respiratory diseases.

At the second stage, the frequency of GERD diagnosed based on the results of different instrumental methods was compared between groups A-B, and calculated totally. Then the relationship between esophageal manifestations of GERD and parameters of these methods were performed.

2.2. Diagnostic criteria and instrumental methods

Diagnostic criteria for RCRD and GERD

Diagnoses of RCRD are established on the basis of appropriate diagnostic criteria, international and Russian conciliatory documents. Respiratory diseases that, despite treatment and prevention, recur for unknown reasons; chronic respiratory diseases often have exacerbations (eg, uncontrolled asthma).

Clinical diagnosis of GERD was carried out in the presence of characteristic clinical symptoms that cause anxiety in the patient over 7 years old using GERD-Q questionnaire, according to which the number of points ≥8 testified to GERD [9,10], or GER equivalents in children under 7 years of age (regurgitation, sleep disturbance, delayed weight gain, irritability, Sandifer syndrome).

Table 1. GERD-Q Questionnaire [9,10]

Questions: during the last week	**0 days**	**1 day**	**2-3 days**	**4-7 days**
	Number of points			
1. How often do you have heartburn?	0	1	2	3
2. How often do you feel the rush of food (liquid or food) from the stomach into the pharynx or mouth (regurgitation)?	0	1	2	3
3. How often do you have upper abdominal pain?	3	2	1	0
4. How often do you get nausea?	3	2	1	0
5. How often do you experience sleep disturbances due to heartburn or regurgitation?	0	1	2	3
6. How often do you take medication to treat heartburn or regurgitation?	0	1	2	3

The number of points ≥8 testified to GERD

The diagnostic criteria for GERD when carrying out instrumental research methods were the following: reflux esophagitis during EGDS [11]; insufficiency of the cardia with the identification of grade 1-4 GER in the X-ray examination of the esophagus with contrast [11]; DeMeester score > 14,72 based on the results of 24-pH [6,11]; DeMeester score > 14,72 and / or impedance reflux > 53 episodes per day with pH-MII [12].

Instrumental methods

pH-MII was performed according to the standard method using an Ohmega-TM instrument. The catheter was selected according to the age of the patient, inserted intranasally in the supine position under the control of esophageal fluoroscopy, and then connected to the recording unit for 24 hours. The following parameters were decoded: by pH-channel - DeMeester score, reflux index; by impedance channel - the total number of refluxes, the number of acid, weakly acid, alkaline refluxes in 24 hours.

Reflux was considered acid at pH <4, weakly acid at 4 ≤ pH <7, alkaline if pH ≥7. Reflux index was defined as the percentage of time at which pH <4. GERD was considered abnormal in infants with a reflux index > 10%, in children over 1 year of age - > 5%.

The criteria for the diagnosis of GERD by the pH channel was the DeMeester score above 14,72 [6,11]; by the impedance channel GERD was confirmed if the daily reflux episodes were more than 53 [12]. This study was carried out in 42 patients at the age of 4 months. - 17 years old (Me – 2,75; IQR 1,08-9,42).

24-hour pH-monitoring: In conditions of impossibility of conducting pH-MII, in children over 1 year old, 24-hour pH-monitoring was carried out using the GastroScan-GEM device. Patients were prepared in the same way as during the pH-MII. The following parameters were decoded: DeMeester score, reflux index. This study was conducted in 20 patients at the age of 1 year and 9 months. - 17 years old (Me – 9,5; IQR 5,2325 – 12,4375).

X-ray esophagus with contrast. The following interpretation of the results was used: no GER - no reflux of gastric contents into the esophagus; insufficiency of the cardia 1st degree - reflux of gastric contents to the lower third of the esophagus, 2nd degree - to the middle third of the esophagus, 3rd degree - to the upper third of the esophagus, 4th degree - to the oropharynx [11]. This study was conducted in 107 patients aged 3 months up to 17 years 8 months (Me 3,92; IQR 1,17-9,42).

EGDS was performed using Fujinon EG-530NW, Fujinon FG-1ZP gastroscopes. The following parameters were performed: reflux esophagitis (catarrhal esophagitis, erosive esophagitis, without pathology) and accompanying upper gastrointestinal tract lesions (insufficiency of the cardia, gastroesophageal prolapse, gastritis, duodenitis). To assess the degree of damage to the esophageal mucosa, we used the classification of reflux esophagitis in children according to G. Tytgat modified by V.F. Privorotsky et al. 2005 [11]. This study was conducted in 82 patients aged 3 months to 17 years 8 months (Me 5,92; IQR 1,67-9,83).

Other methods, including fibrolaryngoscopy, computed tomography of the lungs, bronchoscopy, neonatal screening for cystic fibrosis, sweat test, testing for tuberculosis, immune status, allergostatus, have been used to exclude other diseases, which may aggravate respiratory illness - as listed in exclusion criteria. Depending on the private RCRD disease of each patient, different methods were selected for screening.

2.3. Statistical method

Statistical data processing was performed using Microsoft Excel 2019 and IBM SPSS Statistics 20. Frequencies of the trait were calculated for all qualitative indicators, and the median (interquartile range) was calculated for each of the quantitative indicators in the entire sample and in the study groups. The statistical significance of differences between the frequency indicators of groups with expected frequencies of 5 or more was assessed using the $\chi 2$ test (chi-square). For n <20 or the presence of expected frequencies of 5 or less, Fisher's exact test was used. Normality was tested using the Kolmogorov-Smirnov test (n> 50) or the Shapiro-Wilk test (n <50). The statistical significance of differences between the quantitative indicators of groups with an abnormal distribution or with a small sample was assessed using nonparametric methods. Mann-Whitney U-test was used to assess the statistical significance of differences between 2 independent groups, Wilcoxon rank test - 2 dependent groups, Kruskal-Wallis test - more than 2 groups. At p <0,05, the differences were considered statistically significant.

2.4. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (1964), revised in Edinburgh (2000), approved by the Ethics Committee of the RUDN University. All participants were explained and requested for written informed consent.

3. RESULTS

The study included 125 children (70 boys, 55 girls), aged 3 months to 17 years, median 3,75 years (interquartile range, IQR – 1,21-9,38 years), with RCRD, unexplained poor response to standard therapy.

At the first stage, all 125 patients were divided into 2 groups based on clinical diagnosis - detection of esophageal manifestations of GERD based on the results of a questionnaire survey or identification of disease equivalents (depending on age). Group A consisted of 63 children with esophageal symptoms of GERD or their equivalents, group B - 62 children without them.

Group A and Group B patients were compared in terms of main characteristics. The distribution of patients by age, sex, structure and duration of RCRD is presented in Table 2.

Most of the characteristics, including gender, age (from 1 year to 7 years and from 12 years to 17 years), structure and duration of RCRD, were comparable between the two groups. In addition, in the group of patients with esophageal manifestations, there were more children under the age of 1 year, in whom esophageal manifestations of GERD are not specific and there are many equivalents, for example, irritability, delayed weight gain, Sandifer syndrome, etc. In general, the 2 groups were comparable in terms of the structure of respiratory diseases of the upper and lower respiratory tract. In the group of children with esophageal manifestations of GERD, there were statistically significant more patients with recurrent obstructive bronchitis, and fewer with bronchial asthma.

At the next stages of the study in groups A and B, the frequency of GERD based on the results of instrumental studies was compared.

Table 3 shows the frequency of GERD based on instrumental examination methods in children with RCRD, refractory to standard therapy, in general and depending on the presence of clinical esophageal manifestations of GERD.

Table 2. Distribution of patients by sex, age, structure and duration of RCRD depending on the presence / absence of esophageal manifestations of GERD

Criteria		Group A (with oesophageal symptoms of GERD) n = 63	Group B (without esophageal symptoms of GERD) n = 62	p-value
		n / Total (%)	n / Total (%)	
Age	3 months - <1 year	21 (33)	6 (10)	0,0019*
	1 – <3 years	16 (25)	11 (18)	0,3430
	3 - <7 years	15 (24)	14 (22)	0,7913
	7 - <12 years	5 (8)	17 (27)	0,0053*
	12 – 17 years	6 (10)	14 (23)	0,0509
Sex	Male	40 (63)	30 (48)	0,0928
	Female	23 (37)	32 (52)	0,0928
RCRD structure				
Upper respiratory tract diseases (n = 18)		9 (14)	9 (15)	0,9747
	Chronic pharyngitis	3 (5)	4 (7)	0,6389
	Chronic laryngitis	5 (7)	3 (5)	0,6394
	Recurrent otitis media	0 (0)	2 (3)	0,1677
	Recurrent croup	1 (2)	0 (0)	0,2650
Lower respiratory tract diseases (n = 107)		54 (86)	53 (85)	0,9747
	Bronchopulmonary dysplasia	1 (2)	1 (2)	1
	Recurrent pneumonia	17 (27)	9 (15)	0,1012
	Recurrent bronchitis	7 (11)	6 (10)	0,8559
	Recurrent obstructive bronchitis	13 (20)	4 (7)	0,0345*
	Bronchial asthma	6 (10)	25 (39)	0,0002*
	Obliterating bronchiolitis	8 (12)	6 (10)	0,7220
	Bronchiolitis obliterans with organizing pneumonia	1 (2)	0 (0)	0,2650
	Bronchiectasis	1 (2)	2 (3)	0,7212
Duration of respiratory diseases				
	< 1 year	29 (46)	23 (37)	0,3092
	1-4 years	24 (38)	21 (34)	0,6427
	>4 years	11 (18)	17 (27)	0,2299

Table 3. Frequency of diagnosis of GERD by different methods in children with / without esophageal symptoms

Methods	Group A (with esophageal symptoms) n = 63	Group B (no esophageal symptoms) n = 62	Total n = 125	p-value
	n / Total (%)	n / Total (%)	n / Total (%)	
EGDS	32/43 (74)	27/39 (69)	59/82 (72)	0,6036*
Fluoroscopy	48/54 (89)	39/53 (74)	87/107 (81,3)	0,042*
24-pH	4/9 (44)	1/11 (9)	5/20 (25)	0,127**
pH-MII	24/26 (92)	16/17 (94)	40/43 (93)	1**
Total	58/63 (92)	50/ 62 (81)	108/125 (86,4)	0,0637*

*p-value was calculated using the test: * chi-square, ** Fisher's exact test*

The overall frequency of GERD based on instrumental methods in the examined children, as can be seen from table 3 accounted to 86,4%; in children with esophageal manifestations of GERD - 92%, without them - 81%, without statistically significant differences (p> 0,05). With the maximum frequency, GER was detected using pH-MII (93%), which was 3,7 times more often compared with isolated pH-monitoring. 63 patients were examined by ≥2 methods. EGDS was performed in 43 of 63 patients of group A with esophageal manifestations of GERD, while among 43 patients, 32 cases of GERD were diagnosed, in 11 - no pathology of the esophageal mucosa was detected. In 7 (64%) of these 11 patients, GERD was confirmed by 24-pH or pH-MII and was defined as non-erosive reflux disease (NERD).

A more detailed description of the results of instrumental examinations of patients in groups A and B is presented in Table 4-7.

Table 4 presents the result of fluoroscopy of the esophagus with contrast and water-siphon test in children with RCRD.

Table 4. Frequency of absence of gastroesophageal reflux and degree of cardia insufficiency according to fluoroscopy in children with / without esophageal manifestations of GERD

Fluoroscopy of the esophagus with contrasting	Group A1 (with esophageal symptoms) n = 54	Group B1 (no esophageal symptoms) n = 53	p-value
	n / Total (%)	n / Total (%)	
No gastroesophageal reflux	6 (11)	14 (26)	0,0464*
Insufficiency of the cardia 1st degree	15 (28)	16 (30)	0,8205
Insufficiency of the cardia 2nd degree	9 (17)	13 (25)	0,3117
Insufficiency of the cardia 3rd degree	23 (42)	10 (19)	0,0102*
Insufficiency of the cardia 4th degree	1 (2)	0 (0)	0,3030

p-value was calculated using Chi-square test, Fisher's exact test

Table 5. Visual changes according to esophagogastroduodenoscopy in children with / without esophageal manifestations of GERD

Pathology	Group A2 (with esophageal symptoms) n = 43	Group B2 (no esophageal symptoms) n = 39	p-value
	n / Total (%)	n / Total (%)	
Catarrhal esophagitis	23 (53)	23 (59)	0,587
Erosive esophagitis	6 (14)	2 (5)	0,172
Esophageal stricture	2 (5)	0 (0)	0,159
Insufficiency of the cardia	11 (26)	8 (21)	0,597
Gastroesophageal prolapse	3 (7)	4 (10)	0,627
Gastritis	18 (42)	21 (54)	0,280
Duodenitis	11 (26)	17 (44)	0,089
Without pathology	4 (9)	2 (5)	0,484
Biopsy of the esophageal mucosa, n = 14, abs.			
Barrett's esophagus	1	0	0,323
Reactive changes	0	3	0,059

p-value was calculated using Chi-square test, Fisher's exact test

Table 6. 24-pH parameters in children with / without esophageal manifestations of GERD

24-pH parameters	Group A3 (with esophageal symptoms), n = 9	Group B3 (no esophageal symptoms), n = 11	p-value
	Median (IQR)	Median (IQR)	
DeMeester score	13,18 (5,655-30,17)	3,5 (2,38-6,62)	0,046*
Reflux Index	4,31 (2,085-11,67)	1,04 (0,57-1,95)	0,025*

*p-value * <0,05 calculated using nonparametric Mann-Whitney U-test*

Table 7. The relationship between esophageal manifestations of GERD and GER parameters according to pH-MII data

Indicators	Group A4 (with esophageal symptoms), n = 25	Group B4 (no esophageal symptoms), n = 17	p-value
	Median (IQR)	Median (IQR)	
pH-MII parameters by pH channel			
DeMeester score	29,54 (7,58-56,015)	5,73 (2,66-15,955)	0,003*
Reflux Index	8,5 (2,05-14,8)	1,1 (0,55-4,45)	0,001*
pH-MII parameters by impedance			
General reflux[1]	115,2 (40,7-170,9)	188,8 (122,4-375,9)	0,003*
Acid reflux[1]	40,5 (11,15-90,05)	26,3 (13,35-56,4)	0,311
Weakly acid reflux[1]	51,7 (12,35-88,1)	127,6 (53,3-312)	0,001*
Alkaline reflux[1]	0 (0-4,25)	10,6 (1,75-47,3)	0,001*

*1 number of episodes in 24 hours, 2 seconds, p-value * <0,05 was calculated using the nonparametric Mann-Whitney U-test (pH-MII parameters), IQR - interquartile range*

In children with esophageal manifestations of GERD, insufficiency of the cardia 3rd degree was more often recorded and less often the absence of GER compared with the group of children without esophageal manifestations of GERD.

Visual changes in the mucous membrane of the esophagus, stomach and duodenum and the results of biopsy of the esophagus are presented in Table 5.

From Table 5 it can be seen that with EGDS, catarrhal esophagitis was most often detected (in 46 of 82 patients). Among concomitant diseases, the most frequent were gastritis and duodenitis (in 48% and 34% of patients, respectively). Based on this study, esophageal manifestations of GERD are not associated with the degree of damage to the esophageal mucosa according to the results of EGDS ($p > 0,05$).

Table 6 shows the characteristics of gastroesophageal reflux according to the data of 24-pH.

According to the data of 24-pH in patients with esophageal manifestations of GERD, in comparison with the group without such manifestations, the DeMeester score and reflux index was recorded higher.

The relationship between esophageal manifestations of GERD and GER parameters according to pH-MII data is presented in Table 7.

You can see in Table 7, in patients without esophageal manifestations of GERD, the number of general reflux episodes, episodes of weakly acid, alkaline reflux were statistically significantly more frequent, compared with patients with esophageal manifestations.

Similarly to the results of 24-pH, according to the pH-channel of pH-MII in patients with esophageal manifestations of GERD, the DeMeester score, reflux index were also higher.

4. DISCUSSION

According to the data of the study, GERD was diagnosed in 86,4% of children with RCRD. This result corresponds to the data of previous studies, according to which, short-term (within 2-3 hours) pH-monitoring revealed GERD in 47-100% (on average in 76%) children with recurrent respiratory diseases, long-term pH-monitoring revealed reflux in 92-94% of the examined children with these diseases [13-16]. According to V.F. Privorotsky et al. (2004) in 65% of children with BA, 88% of children with cystic fibrosis and 50% of children with recurrent bronchitis, GERD of varying severity was identified based on clinical, radiological and endoscopic examination methods [17]. Among the patients examined by us, in 81% of children without esophageal manifestations of GERD, pathological GER was confirmed by instrumental methods. The high frequency of detecting GERD in children with RCRD examined by us may be a consequence of an increase in intra-abdominal pressure and an increase in negative pleural pressure during coughing, hyperinflation of lung tissue, as well as the result of the use of bronchodilators, that relax the lower esophageal and pyloric sphincters, which increases the frequency and severity of gastroesophageal and duodenal reflux. GERD and RCRD interact according to the type of a closed pathophysiological circle: irritation of the esophageal mucosa by gastric contents can cause bronchospasm mediated through n. vagus, as well as due to a direct effect on the receptors of the larynx, trachea and bronchi during micro- or macroaspiration of gastric contents, which leads to nonspecific hyperreactivity of the bronchi and the development of an inflammatory process in the tracheobronchial tree [18].

In our study, in order to identify clinical criteria for the diagnosis of GERD in children over 7 years old, we used the GERD-Q questionnaire. In adult patients, GERD-Q is a very valuable questionnaire in the diagnosis of GERD. According to V.O. Kaibysheva et al. (2013) the sensitivity of the questionnaire in adults was 65,4%, specificity – 91,7%, tested by the method of 24-pH [10]. However, GERD-Q assesses only the esophageal symptoms of GERD (heartburn, regurgitation), which are usually caused by acid reflux [19,20], while weakly acid and alkaline reflux, more often associated with non-esophageal manifestations of GERD, as shown in our study (table 7), are detected only by pH-MII [21-23]. In the children examined by us with RCRD, without esophageal manifestations of GERD, according to the results of pH-MII, the most frequent variant of reflux was weakly acid reflux. The obtained result coincides with the results of the study by X. Xu et al. (2014), in which the GERD-Q questionnaire and the pH-MII were used to diagnose GERD in adults with chronic cough. GERD was confirmed in 68 (97,1%) of 70 GERD-Q-positive patients with esophageal symptoms, while most of them (50 of 68, which was 73,5%) had acid reflux verified. In the group of GERD-Q-negative patients who did not have esophageal symptoms, GERD was detected in 34 (60,7%) of 56 patients with a predominance of non-acid GER, including weakly acid and alkaline reflux (29 patients, which was 85,3%). while acid reflux was detected only in 5 (14,7%) patients [24].

According to the data of 24-pH, the overall detection rate of GERD in children with RCRD in our study was low (25%), while in patients with clinical esophageal manifestations of GERD it was 44,4%, in the group of children without them – 9,1%. In comparison with the results of GERD verification by means of 24-pH, the frequency of GERD diagnostics in children with RCRD based on pH-MII was very high (93%). This result is explainable. pH-MII differs from 24-pH in that it has an additional impedance channel. According to this channel, there was currently no unified standard for diagnosing GERD, we used according to the protocol of the programmed machine Ohmega-TM, taking 95th percentile value of daily reflux episodes, which is more than 53 episodes in patients off therapy [12]. The sensitivity of 24-pH in determining alkaline reflux is very low and amounts to 28% [25]. 24-pH assesses acid reflux, while pH-MII records all types of reflux (acid, weakly acid, alkaline). So, according to the results of pH-MII, weakly acid refluxes prevailed in the patients we observed, which were not accompanied by characteristic esophageal symptoms. This can explain the high frequency of GERD-Q-negative patients (49,6%) among patients with RCRD on the background of GERD. Despite the fact that pH-MII is currently regarded as the most informative method for diagnosing GERD, this method is not available in most hospitals, its cost is high, the study lasts 24 hours, causing discomfort in the patient, and if patients have motility disorders and severe esophagitis, then due to a decrease in the baseline impedance values, the pH-MII can underestimate the number of refluxes [6]. For these reasons, the number of patients simultaneously examined by pH-MII and other methods was limited. Another limitation of the study may be the fact that the sample size was not pre-calculated. In this regard, it is impossible to generalize the obtained data for the entire population of patients with RCRD.

According to world studies, non-acid reflux in pediatric practice, especially in children in the first months of life, is a common occurrence, accounting for 45-89% of all reflux episodes [26], which is consistent with our data. There is an opinion that the presence of duodenal contents in refluctate, in other words, the presence of weakly acid or alkaline reflux, detected only with the help of pH-MII, may be the cause of a more severe course of GERD, ultimately complicated by the development of Barrett's esophagus and esophageal adenocarcinoma [27,28]. This provision requires further research based on the study of the long-term follow-up of patients. Thus, pH-MII is an indispensable method for diagnosing GERD in children with RCRD.

According to our study, changes in the esophageal mucosa and clinical esophageal manifestations of GERD are not related to each other. According to Y. Vandenplas et al. (2019) there are no specific symptoms of esophagitis [29]. Even in patients with Barrett's esophagus, severe clinical symptoms have not been reported [30].

Conclusion

In children with RCRD, refractory to standard therapy, the frequency of GERD was high. It is possible to screen for GERD in children with RCRD, independent on the presence of clinical esophageal symptoms of GERD.

AUTHOR CONTRIBUTIONS

VBN participated in the study design, execution, analysis, manuscript drafting, critical discussion and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Privorotsky V.F, Luppova N.Ye. [Gastroesophageal reflux disease in children]. In the book: Pediatric gastroenterology, a practical guide. Ed. I.Yu. Melnikova. M. GEOTAR-Media, 2018:184-203. Russian.
2. Abdallah A, El-Desoky T, Fathi K, Fawzi Elkashef W, Zaki A. Evaluation of gastro-oesophageal reflux disease in wheezy infants using 24-h oesophageal combined impedance and pH monitoring. Arab J Gastroenterol. 2017 Jun;18(2):68–73.
3. Kahrilas PJ. Gastroesophageal Reflux Disease. JAMA. 1996 Sep;276(12):983–8.
4. Koufman J. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal. Laryngoscope. 1991 Apr;101(4):1–78.
5. Klaus A, Swain JM, Hinder RA. Laparoscopic antireflux surgery for supraesophageal complications of gastroesophageal reflux disease. Am J Med. 2001 Dec;111(8A):202S–206S.
6. Rosen R, Vandenplas Y, Singendonk M, Cabana M, Di Lorenzo C, Gottrand F, Gupta S, Langendam M, Staiano A, Thapar N, Tipnis N, Tabbers M. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2018 Mar;66(3):516–54.
7. Tutuian R, Castell DO. Multichannel intraluminal impedance: General principles and technical issues. Gastrointest Endosc Clin N Am. 2005 Apr;15(2):257–64.
8. Privorotsky V.F., Luppova N.E., Belmer S.V., Apenchenko Yu.S., Basalaeva N.V., Gurova M.M., et al. [Working protocol for the diagnosis and treatment of gastroesophageal reflux disease in children]. Children's Hospital.2013 Mar;1:54-61. Russian.
9. Jones R. et al. Development of the GERD-Q, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary – care. Aliment Pharmacol Ther. 2009 Nov; 30(10):1030-1038.
10. Kaibysheva V.O., Kucheryavyy Yu.A., Trukhmanov A.S., Storonova O.A., Konkov M.Yu., Maev I.V. et al. [Results of a multicenter observational study on the use of the international GERD-Q questionnaire for the diagnosis of gastroesophageal reflux disease]. Russian journal of gastroenterology, hepatology, coloproctology. 2013 Sep-Oct;5:15-23. Russian.
11. [Gastroesophageal reflux disease in children. Clinical guidelines. Union of Pediatricians of Russia, 2016]. https://www.pediatr-russia.ru/sites/default/files/file/kr_grb.pdf. (date of access: 01.07.2019). Russian.
12. Zerbib F, Roman S, Bruley S, Varannes DES, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F and the Groupe Francais De Neuro-Gastroenterologie. Normal Values of Pharyngeal and Esophageal 24-Hour pH Impedance in Individuals on and off Therapy and Interobserver Reproducibility CONCLUSIONS : YJCGH. 2013 Apr;11(4):366–72.
13. Shapiro G., Christie D. Gastroesophageal reflux in steroid-dependent asthmatic youths // Pediatrics. 1979 Feb;63(2):207-212.
14. Foglia RP, Fonkalsrud EW, Ament ME, Byrne WJ, Berquist W, Siegel SC, Katz RM, Rachelefsky GS. Gastroesophageal fundoplication for the management of chronic pulmonary disease in children. Am J Surg. 1980 Jun;140(1):72–9.
15. Jolley S, Herbst J, Johnson D, Matlak M, Book L. Esophageal pH monitoring during sleep identifies children with respiratory symptoms from gastroesophageal reflux. Gastroenterology. 1981 Jun;80(6):1501–6.
16. Barish CF, Wu WC, Castell DO. Respiratory Complications of Gastroesophageal Reflux. Arch Intern Med. 1985 Oct;145:1882–8.
17. Privorotsky V.F., Luppova N.E., Gerasimova T.A., Orlov A.V., Romanyuk F.P., Antonova E.A. [Diseases of the respiratory tract in children associated with gastroesophageal reflux]. RMJ. 2004 Feb;3:129. Russian.
18. Bryksina E.Yu., Pochivalov A.V., Bryksin V.S., Zhidkov M.L., Kryukov Yu.V., Savchenko A.P. Clinical and pathogenetic significance of microaspiration of gastric contents in the development and course of bronchopulmonary dysplasia. Pediatrics. 2014 Sep; 93 (1): 51-56. Russian
19. Savarino E, Tutuian R, Zentilin P, Dulbecco P, Pohl D, Marabotto E, Parodi A, Sammito G, Gemignani L, Bodini G, SavarinoV. Characteristics of Reflux Episodes and Symptom Association in Patients With Erosive Esophagitis and Nonerosive Reflux Disease : Study Using Combined Impedance – pH Off Therapy. Am J Gastroenterol. 2010 May;105(5):1053–61.
20. Bredenoord AJ, Weusten BLAM, Curvers WL, Timmer R, Smout AJPM. Determinants of perception of heartburn and regurgitation. 2006 Mar;55(3):313–8.
21. Magista AM, Indrio F, Baldassarre M, Bucci N, Menolascina A, Mautone A, Francavilla R. Multichannel intraluminal impedance to detect relationship between gastroesophageal reflux and apnoea of prematurity. Dig Liver Dis. 2007 Mar;39:216–21.
22. Blasco-Alonso J, Yun-Castilla C, Girón-Fernández-Crehuet F, Peláez-Cantero MJ, Serrano-Nieto J, Navas-López VM, Sierra-Salinas C. Esophageal multichannel intraluminal impedance and pH-testing in the study of apparent life threatening episode incidents in infants. 2014 Mar;106:159–64.
23. Tack J, Blondeau K. Weakly Acidic Reflux. Dig Dis. 2009 May;27:58–61.

24. Xu X, Chen Q, Liang S, Lv H, Qiu Z. Comparison of Gastroesophageal Refl ux Disease Questionnaire and Multichannel Intraluminal Impedance pH Monitoring in Responsive to Antirefl ux Therapy. Chest. 2014 Jun;145(6):1264–70.
25. Hila A, Agrawal A, Castell DO. Combined Multichannel Intraluminal Impedance and pH Esophageal Testing Compared to pH Alone for Diagnosing Both Acid and Weakly. Clin Gastroenterol Hepatol. 2007 Feb;5:172–7.
26. Vandenplas Y, Salvatore S, Devreker T, Hauser B. Gastro-oesophageal reflux disease: Oesophageal impedance versus pH monitoring. Acta Paediatr Int J Paediatr. 2007 Jul;96(7):956–62.
27. Hirota W, Loughney T, Lazas D, Maydonovitch C, Rholl V, Wong R. Specialized intestinal metaplasia, dysplasia, and cancer of the esophagus and esophagogastric junction: prevalence and clinical data. Gastroenterology. 1999 Feb;116(2):277–85.
28. Zimmerman Ya.S. [Clinical gastroenterology: selected sections]. M .: GEOTAR-Media, 2009: 10-39. Russian
29. Vandenplas Y., Hauser B., Salvatore S. Diagnosis and management of gastroesophageal reflux disease in infants and children: from guidelines to clinical practice // Pediatrics. Concilium Medicum. 2019 Mar; 3:14-23.
30. Vandenplas Y., Hauser B. An updated review on gastro-esophageal reflux in pediatrics // Expert Rev. Gastroenterol. Hepatol. 2015 Sep; 9(12):1511–1521.