MedPharmRes

Journal of University of Medicine and Pharmacy at Ho Chi Minh City
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Original article

Gastroesophageal reflux in children with recurrent and chronic respiratory diseases: non-acid or acid?

Van Bich Nguyen[ab*]

[a]*Tay Nguyen University, 567 Le Duan, Buon Ma Thuot City, Dak Lak province, Vietnam;*
[b]*RUDN university, 6 Miklukho-Maklaya, Moscow, Russia.*

Received January 07, 2022: Revised May 10, 2022: Accepted May 12, 2022

Abstract: ***Introduction***: In some cases, gastroesophageal reflux (GER) may be accompanied by duodenogastric reflux, forming non-acid reflux, which has a certain influence on the clinical presentation and the response to anti-reflux therapy. The study aimed to determine the role of non-acid reflux in children with recurrent and chronic respiratory diseases (RCRD). ***Methods***: All children with RCRD, for unknown reason, poorly responding to respiratory-specific therapy, hospitalized for gastroesophageal reflux disease (GERD) screening, using dual pH-multichannel intraluminal impedance (pH-MII). ***Results***: The study was conducted in 42 children at the age Me – 2.75; IQR 1.08-9.42. The most common type of reflux was weakly acid reflux - 62.25 [36.425-121.225], then acid - 34.05 [12.875-71.65], alkaline - 1.75 [0 - 12.375] episodes per day ($p < 0.05$). Non-acid reflux was more common in children with only respiratory symptoms - no esophageal manifestations of GERD. All types of refluxes were more often recorded in the upright compared to the supine position. In 70% patients, cough could be associated with reflux, while in 88% children reflux was non-acid (including 69% - weakly acid, 19% - alkaline), in 38% - acid. ***Conclusions***: Non-acid reflux is the main type of GER in children with RCRD refractory to standard therapy, which could be associated with cough in this patient population.

Keywords: GERD; respiratory diseases; non-acid reflux; children; pH-MII.

1. INTRODUCTION

Gastroesophageal reflux disease (GERD), in addition to esophageal manifestations, also has extraesophageal features, of which the most common is respiratory symptoms. Illnesses that have been identified as associated with GERD such as cough, laryngitis, bronchial asthma, erosion of tooth enamel, some diseases that are believed to be associated with GERD, including pharyngitis, sinusitis, idiopathic lung fibrosis, recurrent otitis [1]. It is remarkable, however, that in many patients, esophageal manifestations are completely absent, and respiratory symptoms seem to be the only manifestation of GERD. According to studies in infants with chronic respiratory symptoms and broncho-obstructive syndrome, latent GERD was recorded in 42-50% [2]. One-third to one-half of patients with bronchial asthma and GERD do not have gastrointestinal manifestations of GERD [3]. This problem makes it difficult to find the cause of respiratory disease (RD) and treat it thoroughly.

Once an association between GERD and RD was established, GERD treatment was developed to improve respiratory symptoms. However, acid reflux still receives the most attention among the reflux types, and current treatment (inhibitors proton pump - IPP, antacids) is focused on it. IPP are effective in treating typical symptoms of GERD; but the results of treatment with GERD with atypical clinical presentation are contradictory [4-6]. In contrast to these data,

*Address correspondence to Van Bich Nguyen at the Tay Nguyen University, 567 Le Duan, Buon Ma Thuot City, Dak Lak province, Vietnam or RUDN university, 6 Miklukho-Maklaya, Moscow, Russia; E-mail: bichvanttat@gmail.com

DOI: 10.32895/UMP.MPR.7.1.1

surgical interventions (fundoplication) gave good results in patients with both typical and atypical manifestations of GERD [7]. So what is the reason for this result? When dual pH-multichannel intraluminal impedance (pH-MII) came out, it cleared up some questions. The problem lies in the less noticeable type of reflux – non-acid reflux. IPP do not relieve this type of reflux, but surgery will cut off the mechanism of GERD, which is highly effective in improving respiratory symptoms. What type of reflux will greatly affect a patient's response to treatment.

The aim of the study was to determine the role of non-acid reflux in children with recurrent and chronic respiratory diseases (RCRD).

2. MATERIALS AND METHOD

2.1. Study population

All children with RCRD, for unknown reason, poorly responding to respiratory-specific therapy, hospitalized at the Department of Thoracic Surgery of the Morozovskaya Children's City Clinical Hospital (MCCC hospital) from November 2017 to September 2019, were included in the study. This is 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; using anti-reflux therapy during pH-MII progression.

Method pH-MII was performed to determine: the typical reflux type in the RCRD patient population; the relationship between acidity of reflux and clinical manifestations (between 2 groups with and without esophageal manifestations of GERD); the accociation between age, the duration of respiratory disease and reflux variants, the patient's position and the amount and type of reflux; and the causal relationship between reflux and cough based on symptom index (SI) and/or symptom association probability (SAP).

2.2. Diagnostic criteria and instrumental methods

Diagnostic criteria for RCRD

Diagnosis of RCRD was based on appropriate diagnostic criteria, international and Russian conciliatory documents. RD that, despite treatment and prevention, recur for unknown reasons; chronic RD often have exacerbations (uncontrolled asthma).

Chronic cough is defined as a cough that lasts more than 8 weeks for dry cough, or more than 4 weeks for wet cough [8].

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 (0-1 years old, 1-3 years old, 3-7 years old, > 7 years), inserted intranasally in the supine position under the control of esophageal fluoroscopy (in children less than 1 year old, the pH electrode was placed 3–4 cm above the lower esophageal sphincter - LES; in children 1-3 years old - by 5 cm; in children older than 3 years, the first pH electrode was placed 5 cm above the LES), and then connected to the recording unit for 24 hours. The following parameters were decoded: by pH-channel - DeMeester score, reflux index, the number of acid reflux; by impedance channel - the total number of refluxes, the number of acid, weakly acid, alkaline refluxes in 24 hours, SI, SAP.

Reflux was considered acidic at pH <4, weakly acidic at 4 ≤ pH <7, alkaline if pH ≥7. Reflux index was defined as the percentage of time at which pH <4. Acidic, weakly acidic, alkaline reflux was considered pathological if the number of reflux episodes in 24 hours was more than 40, 21, 0, respectively [9]. Weakly acid and alkaline reflux are termed non-acid reflux [10,11].

SI (symptom index) describes the proportion of symptoms associated with reflux episodes and is considered positive if > 50%.

SAP (Symptom association probability) describes the likelihood that the observed association between symptoms and reflux is not random, considered positive if it is > 95%.

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. For all qualitative indicators, the frequency of occurrence of the trait was calculated, and for each of the quantitative indicators in the entire sample and in the study groups, the median was calculated (25% quartile, 75% quartile). Normality was checked using the Kolmogorov-Smirnov test (n> 50) and 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 two independent groups, Wilcoxon rank test for 2 dependent groups. At p <0.05, the differences were considered statistically significant.

2.4. Ethical considerations

This is the research result of Van Bich Nguyen 's doctoral thesis, conducted in Russia, at MCCC hospital, the training base of the Department of Pediatrics - RUDN University.

MCCC hospital: The largest children's hospital in Russia and Europe. Located on nine hectares in the historical center

of the capital, in its spirit it resembles a small city. Bed capacity is 1205 beds. This is a multidisciplinary (31 profile) clinical hospital and has 48 departments, including 34 clinical ones. In the MCCC hospital work more than 700 doctors, more than 900 employees from the middle medical staff. Since 2015, the Morozov Children's Hospital has received a license to carry out educational detail and has become the Center for Postgraduate Pediatric Education.

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 under protocol № 13 on December 19, 2019; with written consent from the child's parents or guardians.

3. RESULTS

This study was carried out in 42 children at the age of 4 months - 17 years old (Me – 2.75; IQR 1.08-9.42), with RCRD, unexplained poor response to standard therapy, undergoing pH-MII. The main characteristics of patients are presented in table 1.

Table 1. The main characteristics of the studied patient population

Characteristics	**Children with RCRD, n=42**
Age	4 months - 17 years old Me – 2.75, [IQR 1.08-9.42]
Male/Female	26/16
Structure of RCRD	**n/total (%)**
Chronic pharyngitis	2 (5)
Chronic laryngitis	1 (2)
Recurrent otitis media	1 (2)
Recurrent croup	0 (0)
Bronchopulmonary dysplasia	0 (0)
Recurrent pneumonia	11 (26)
Recurrent bronchitis	5 (12)
Recurrent obstructive bronchitis	9 (22)
Bronchial asthma	5 (12)
Obliterating bronchiolitis	6 (14)
Bronchiolitis obliterans with organizing pneumonia	0 (0)
Bronchiectasis	2 (5)

Table 2. Variants of gastroesophageal reflux in children with recurrent and chronic respiratory diseases, number of reflux episodes (n = 42)

Reflux variants	**Median (IQR)**	**p-value**
Acid	34.05 (12.875-71.65)	Acid-Weakly acid: 0.010*
Weakly acid	62.25 (36.425-121.225)	Weakly acid - Alkaline <0.001 *
Alkaline	1.75 (0 - 12.375)	Alkaline-acidic <0.001 *

**p <0.05 (Wilcoxon nonparametric rank test), IQR - interquartile range*

Table 3. Relationship between esophageal manifestations of GERD in children with recurrent and chronic respiratory diseases and reflux variants

Indicators	**With esophageal symptoms, n = 25**	**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*
Acid reflux	84 (34.4-188.1)	26.7 (11-47.1)	0.003*
pH-MII parameters by impedance channel			
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*
Reflux variants according to pH-MII data, frequency			
	n (%)	n (%)	
Pathological acid reflux[2]	13 (52)	7 (42)	0.491
Pathological weakly acid reflux[2]	16 (64)	17 (100)	0.006*
Pathological alkaline reflux[2]	8 (32)	15 (88)	<0.0001*

*[1]Number of episodes in 24 hours, [2] number of patients with pathological reflux, p * <0.05 was calculated using the nonparametric Mann-Whitney U-test (pH-MII parameters), Chi-square test (frequency of pathological acid and alkaline reflux), Fisher's exact test (frequency of pathological weakly acid reflux); IQR - interquartile range*

Gastroesophageal reflux (GER) options for the acidity of refluctate are presented in Table 2

Thus, in the population of examined patients with RCRD, the most common type of reflux is weakly acid reflux: 62.25 [36.425-121.225] (normal ≤ 21), the second most frequent type of reflux is acid: 34.05 [12.875-71.65] (normal ≤ 40) and, finally, alkaline was the least common: 1.75 [0 - 12.375] (normal = 0, p <0.05). However, in this case, weakly acid and alkaline reflux were pathological, and the median of acid reflux was within the normal range.

Table 3 shows the relationship between the presence of esophageal clinical manifestations of GERD and the variant of GER.

In patients without esophageal manifestations of GERD, in other words, in children with only respiratory symptoms, general reflux episodes, episodes of weakly acid, alkaline reflux were statistically significantly higher; pathological non-acid (weakly acid and alkaline) reflux were more frequent than in group with esophageal symptoms. Besides, one patient may have different types of pathological reflux at the same time.

According to the pH channel of the pH-MII, the DeMeester score, reflux index and acid refluxes were higher in patients with esophageal manifestations of GERD.

Besides, we also compared the results pH-MII based on the patient's age and the duration of respiratory disease in children, the results are presented in Table 4,5.

Table 4. Relationship between age and reflux variants, number of refluxes (n = 42)

Reflux variants	<3 years old n = 20	>3 years old n = 22	p-value
	Median (IQR)	Median (IQR)	
pH-MII parameters by pH channel			
DeMeester score	23.54 (6.2875 – 46.0975)	8.995 (3.255 – 31.3525)	0.217
Reflux Index	6.15 (1.55 -14.175)	2 (0.7 -8.5)	0.137
Acid reflux	75.9 (29.9 – 126.7)	44.9 (13.55 -87.775)	0.124
pH-MII parameters by impedance channel			
General reflux[1]	136.35 (29.8 – 187.4)	172.85 (70.55 – 310.775)	0.059
Acid reflux[1]	36.65 (9.6 – 90.425)	33.75 (15.05 – 69.075)	0.880
Weakly acid reflux[1]	59 (12.7 – 104.025)	86.7 (48.75 – 277.95)	0.092
Alkaline reflux[1]	0 (0 – 3.2)	5.95 (0 – 34.45)	0.009*

*[1]Number of episodes in 24 hours, p * <0.05 was calculated using the nonparametric Mann-Whitney U-test; IQR - interquartile range*

Table 5. The duration of respiratory disease and reflux variants, number of refluxes (n = 42)

Reflux variants	Duration of RD <1.5 years n = 21	Duration of RD >1.5 years n = 21	p-value
	Median (IQR)	Median (IQR)	
pH-MII parameters by pH channel			
DeMeester score	21.16 (6.615 – 42.95)	8.77 (3.08 – 37.99)	0.285
Reflux Index	5.8 (1.7 – 12.9)	1.9 (0.475 – 10.55)	0.247
Acid reflux	67.8 (34 – 175)	44.9 (12.7 – 87.7)	0.056
pH-MII parameters by impedance channel			
General reflux[1]	161.5 (41.3 – 233.45)	136.3 (67.65 – 211.6)	0.950
Acid reflux[1]	54.5 (14.25 – 93.1)	17.3 (11.3 – 55.05)	0.064
Weakly acid reflux[1]	61.3 (16.6 – 115.6)	63.2 (38.6 – 146.3)	0.489
Alkaline reflux[1]	1.4 (0 – 11.65)	2.1 (0 – 16.7)	0.712

*[1]Number of episodes in 24 hours, p * <0.05 was calculated using the nonparametric Mann-Whitney U-test; IQR - interquartile range*

Table 6. Body position and reflux variants, number of refluxes (n = 42)

Reflux variants	Upright position Median (IQR)	Supine position Median (IQR)	p-value
All reflux episodes	95.75 (32.375-155.375)	30.5 (10-64.65)	0.004*
Acid reflux	20.7 (6.425-37.1)	8.35 (2.45-18.875)	0.039*
Weakly acid reflux	34.5 (14.025-94.05)	13.8 (4.675-37.275)	0.006*
Alkaline reflux	1.05 (0-9.95)	0 (0-1.1)	0.037*

*p * <0.05 (Wilcoxon test), IQR - interquartile range*

The group of children > 3 years old recorded more alkaline reflux, the remaining types of reflux did not differ with statistical significance. And in terms of duration of respiratory illness, there was no difference between the group with respiratory disease lasting more than and less than 1.5 years.

A comparison of GER in upright and supine positions is presented in Table 6.

All reflux episodes, episodes of acid, weakly acid and alkaline reflux were more often recorded in the upright position compared to the supine position (p <0.05).

pH-MII allowed us to identify a causal relationship between extraesophageal symptoms (cough) and reflux. In 37 out of 42 children with RCRD, examined using pH-MII, cough was recorded during the study, in which 20 patients had chronic cough.

Table 7. Relationship between cough and reflux variants, number of patients

Positive parameters	**Reflux variants**			**Total N = 37**	**Chronic cough** (n=20)	
	Acid reflux	**Weakly acid reflux**	**Alkaline reflux**		**Dry n=17**	**Wet n=3**
	n (%)	n (%)	n (%)	n (%)		
SI	0	7	0	12		
SAP	10	14	5	23		
SI and SAP	**10 (38)**	**18 (69)**	**5 (19)**	**26 (70)**	16	3

SI - symptom index, SAP - index of possible association of symptoms and reflux. In this study, to assess the causal relationship with gastroesophageal reflux, the symptom noted during the pH-MII measurement was cough

In 26/37 (70%) patients, cough was associated with reflux, while in 18 (69%) children refluxes were weakly acid, in 10 (38%) - acid and in 5 (19%) - alkaline.

Moreover, in 19 out of 20 patients, chronic cough was associated with reflux, including in 3/3 children with wet cough and in 16/17 with dry cough. 3 patients with chronic wet cough had the following diagnoses: bronchiectasis (1 patient), recurrent pneumonia (1), recurrent obstructive bronchitis (1); and 16 patients with chronic dry cough had: recurrent obstructive bronchitis (5), recurrent pneumonia (2), recurrent bronchitis (2), bronchial asthma (2), obliterating bronchiolitis (1), bronchiectasis (1), chronic pharyngitis (1), chronic laryngitis (1), recurrent otitis media (1).

4. DISCUSSION

The leading variant of reflux in children with RCRD was weakly acid. In a subgroup of patients without esophageal symptoms of GERD, in whom respiratory manifestations were the only manifestations of reflux, weakly acid reflux and alkaline reflux, forming non-acid reflux, were the main options. 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 [12], which is consistent with our data. According to the pH-channel, in patients with esophageal manifestations, the DeMeester score, the reflux index, the number of acid reflux were higher ($p<0.05$). In other words, acid reflux is more common for the esophageal manifestations of GERD. Moreover, according to S. Kunsch, T. Linhart et al. (2008), A. Gasiorowska, T. Navarro-Rodriguez (2009), D.M. Nguyen et al. (2009) the role of alkaline reflux in the formation of resistant GERD, the development of Barrett's esophagus with subsequent transformation into adenocarcinoma of the esophagus was confirmed [13-15]. According to G.N. Tarasova, E.A. Smirnov (2017), in adult patients with acid and weakly acid reflux, erosive esophagitis of grades A and B prevailed, in the group with alkaline and weakly alkaline reflux - erosive esophagitis C, D and Barrett's esophagus [16]. Thus, non-acid reflux may be associated with a worsening of the course and prognosis of GERD both from the esophagus and from the respiratory tract [13-15,17].

In Table 3, generally, 20 (47.6%) children with RCRD had pathological acid reflux, 33 (78.6%) - pathological weakly acid reflux and 23 (54.8 %) - pathological alkaline reflux. Especially, in group children without esophageal symptoms: 100% had pathological weakly acid, and a large proportion (88%) - pathological alkaline reflux. In other words, pathological non-acid was more common in children with RCRD, especially in the group without gastrointestinal manifestations of GERD. This result may explain why reflux surgery is more effective at relieving typical, especialy atypical symptoms of GERD (respiratory) than antireflux drug (IPP, antihistamin H2) [4-7]. S.J. Sontag et al. (2003) conducted a controlled study involving 62 patients with asthma and reflux. At a 2-year follow-up, the authors concluded that, 74.9% of patients showed an improvement in asthma symptoms after surgery, compared with patients who received ranitidine treatment (improvement in only 9.1% of patients) [18]. Antihistamin H2 and IPP increase pH and decrease gastric volume, the pH of the reflux during this therapy will generally be between 5 and 7, being weakly acidic [19]. IPP have no direct effect on pepsin secretion, and this cannot prevent reflux [20]. Therefore, during IPP treatment, gastric juice will still contain other damaging components. This helps to explain the observation that antisecretory treatment has generally failed in most patients with chronic cough [21]. Atypical symptoms of GERD are largely due to non-acid refluxes (pH>4), or the high acidity of the refluxate does not play an important role in their occurrence. At the same time, IPP mainly reduce the acidity of the refluxate, and do not break the pathogenetic chain. During IPP treatment, the total number of refluxes did not decrease, and acid refluxes turned into non-acid ones [22.23]. On the other hand, surgery restores the function of the LES, which prevents the flow of reflux. Thus, the problem of both acid and non-acid reflux is solved.

A patient can simultaneously have several forms of pathological reflux: acid, non-acid (depending on the number of reflux episodes per day). Patients were treated according to the type of pathological reflux recorded: if patient had only pathological acid reflux, they treated by IPP, antacids; if there was pathological non-acid reflux ± pathological acid reflux: IPP, antacids, motilium and ursodeoxycholic acid, which reduce the harmful effects of bile salts on the esophageal mucosa.

As noted above, weakly acid reflux is the leading type of GER in children with RCRD. A more detailed analysis showed that, the number of weakly acid refluxes did not differ between patients of different ages, although alkaline reflux was more commonly reported in children over 3 years old. Overall, 45-90% of infant reflux episodes are non-acid due to the buffering effect of frequent breast milk feedings [12]. Since newborns and infants feed frequently, almost every 2-3 hours, their reflux contains food, milk or formula, and not

stomach acid [24]. So, in younger children, the rate of non-acid reflux is higher. According to the results of our study in patients with RCRD, the main type of reflux for all ages is non-acid. When comparing between two groups <3 and > 3 years old, even the group > 3 years old had more weakly acid reflux (although $p>0.05$), while alkaline reflux was significantly more ($p<0.05$). In patients with RCRD in general, the typical type of reflux is non-acid, independent of age. However, further studies across age groups are needed to reach definitive conclusions. Due to the small sample size, to ensure statistical significance, it was not possible to divide into more age groups such as 0-1 years old, 1-3 years old, 3-7 years old, > 7 years old for research. This is a limitation of our study.

The relationship between the duration of respiratory illness and GER is poorly understood. According to our data, there was no difference in acidity of refluctate in children with duration of RD less and more than 1.5 years. Thus, non-acidic reflux is the main type for children with RCRD, regardless of age and duration of RD.

In our study, general reflux episodes, acid, weakly acid, alkaline reflux were recorded more in the upright position ($p <0.05$). The result obtained corresponds to the result in healthy children [9]. Children are more active in a standing position, so they may have increased intra-abdominal pressure. At night, the pressure in the lower esophageal sphincter is increased, the sphincter is in a closed state [25]. Only 0.3% of healthy people have GER present at night [15]. Affecting the severity of GERD is not only the number of reflux episodes, but also the composition, volume of refluctate; clearance of the esophagus (time to clear the esophagus from refluctate); the number of prolonged reflux episodes [7, 26]. Upright position improves the process of gastric emptying, cleansing the esophagus from gastric contents, and helps to reduce the risk of aspiration of gastric contents into the respiratory tract. In other words, this position will shorten the contact time of the esophagus with refluctate, but in fact the number of refluxes will not decrease.

According to our data, in 70% patients, cough could be associated with reflux, of which most often (88%) ware related to non-acid reflux (including 69% - weakly acid, 19% - alkaline), in 38% of cases - to acid reflux. The number of studies of GERD in children using SI or SAP/pH-MII is very limited, in particular, the relationship between clinical manifestations and the type of reflux is poorly understood. All studies on the typical symptoms of GERD have been conducted in adults. Only 3 studies of atypical manifestations (respiratory manifestations) of GERD have been performed in children. In H. Mousa's study (USA, 2005) in 25 children aged 1-19 months [27], A.M. Magista (Italia, 2007) – 6 children / 7-28 days [28]; MT. Hernani (Spain, 2012) – 49 children/ 3-16 years old [29]; the rate of respiratory manifestations (cough, sore throat) related to acid reflux was 46.25%; 30.51%; 32% respectively. Consistent with our results.

However, the problem of registering symptoms in children remains. There are many steps that create error: forget to record symptoms, delay between the onset and the recording of symptoms on the machine, or symptoms may occur during sleep. The intraesophageal pressure recorder (IEPR) detected 94% of all cough episodes, but only 48% of which were reported by patients/parents. Using IEPR as the standard criterion for cough detection, the reliability of a patient's report of cough detection is 46% [30].

When analyzing MII-pH results, in patients with esophageal dysmotility or severe esophagitis, including both computerized and manual analysis, the number of reflux episodes may underestimate because of low base resistance. Although a low baseline impedance may alert the clinician to the presence of esophagitis, it does not preclude the need for esophagogastroduodenoscopy (EGDS) [31,32]. EGDS was included in the study, but due to the purpose of the paper, data on this method were not included here.

Method pH-MII is not available in most hospitals, expensive and is an invasive, 24-hour procedure, so the sample size was small. This is the limitation of this study.

No general conclusions can be drawn for all patient, but only for children with RCRD who are poorly responsive to respiratory-specific therapy.

From the results of the study, we have the following recommendations: Should conduct GERD screening in children with RCRD. Depending on the MII-pH results, a corresponding treatment strategy and an appropriate prognosis for the patient are proposed. If the patient has acid reflux - treat as typical GERD, the prognostic outcome is good. If it is non-acid reflux, medical treatment requires more motilium, ursodeoxycholic acid; the prognosis is not good; consider antireflux surgery.

Conclusion

Our study indicated that the main type of gastroesophageal reflux in children with RCRD, refractory to standard therapy is non-acid relfux, which may be associated with respiratory symptoms (cough). However, non-acid reflux responds poorly to antisecretory treatment (IPP, antihistamin H2, antacids), leading to the future challenge to find drugs that are effective for both acid and non-acid reflux, in addition to antireflux surgery.

To improve the diagnostic ability of the causal relationship between reflux and respiratory symptoms (cough), concurrent use of intraesophageal pressure recorder (IEPR) and MII-pH is recommended.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGEMENTS

I would like to offer my special thanks to my scientific adviser MD Ovsyannikov D.Y. and colleagues from the Department of Thoracic Surgery at Morozovskaya Children's City Clinical Hospital for their expertise and assistance throughout all aspects of our study.

AUTHORS' CONTRIBUTION

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

ORCID ID

Van Bich Nguyen https://orcid.org/0000-0001-5611-8604

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