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Assessment of Clinical Symptoms and Multichannel Intraluminal Impedance and pH Monitoring in Children After Thoracoscopic Repair of Esophageal Atresia and Distal Tracheoesophageal Fistula

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. Motility disturbances of the esophagus and gastroesophageal reflux disease (GERD) are observed frequently in children after repair of congenital esophageal atresia with distal tracheoesophageal fistula (EA/TEF). Recently, in many pediatric surgical centers, thoracoscopic repair was introduced, which theoretically would change the postoperative course.

Objectives. The goal of the study was to assess physical development, disease symptoms, and GERD symptom frequency in children who underwent thoracoscopic surgery of congenital EA/TEF.

Material and Methods. The study comprised 22 children (14 boys and 8 girls), aged 16 to 79 months (average age 47.3 months) after surgery of EA/TEF. Clinical symptoms and physical development were analyzed. In 19 children, multichannel intraluminal esophageal impedance connected with pH-metry (MII/pH) was performed. In 11 patients, esophagogastroduodenoscopy with a histological study of mucosa samples was done.

Results. The most frequent symptoms were dysphagia, belching, cough and recurrent bronchitis. In 31.5% of the children, body mass deficiency was observed and in 28.6%, low body mass and short stature. Prematurity was present in half of the patients. Depending on the result of the MII/pH study, the children were divided into two groups: 10 children with GERD and 9 children without diagnosis of gastroesophageal reflux. In the 10 with GERD, acid reflux was diagnosed in 9 and non-acid reflux was diagnosed in one. MII/pH demonstrated statistically significant differences in the number of reflux episodes, reflux index, bolus exposure index, mean time of esophageal exposure and acid exposure and mean acid clearance time in children with GERD in comparison to children without this disease. In 36.4% of children who underwent endoscopy, esophagitis was diagnosed, esophageal stricture in 18% and gastric metaplasia in 9.1%.

Conclusions. In children who underwent corrective thoracoscopic surgery of EA/TEF, GERD caused by motility disorders of the esophagus was frequently observed. These children require constant monitoring and early treatment of the complication (**Adv Clin Exp Med 2016, 25, 5, 917–922**).

Key words: esophageal atresia, tracheoesophageal fistula, thoracoscopy, gastroesophageal reflux disease, MII/pH.

Multichannel intraluminal impedance (MII) was first described by Silny in 1991 [1]. The principles of impedance testing are based on the measuring of differences in resistance to alternating current of the intraluminal contents, which permits the detection of bolus transit [2–4]. Twenty-four-hour measurement of multichannel intraluminal esophageal impedance connected with pH-metry (MII/pH) makes possible the assessment of pH and other parameters of gastroesophageal reflux

together with disease symptoms and the diagnosis of gastroesophageal reflux disease [5–7].

Congenital esophageal atresia with distal tracheoesophageal fistula (EA/TEF) is a condition in which a part of the esophagus is not developed. According to Ladd, four types of atresia can be distinguished, with type III being the most frequent (esophageal atresia with distal tracheoesophageal fistula, 86%) [8]. Moreover, rare cases of congenital esophageal stenosis can occur [9]. In children with congenital esophageal atresia, other congenital malformations are frequently present. According to Pedersen et al. [10], the prevalence of EA/TEF, calculated based on the European registry EUROCAT in 23 European regions during the years 1987–2006 was 2.43 per 10,000 births and it was stable in both decades studied. In 31.6% of cases, esophageal atresia was accompanied by numerous other congenital malformations and the most frequent among them were: malformations of the genitourinary tract, heart disorders, disorders of the skeleton, anal atresia and duodenal atresia. In 23.7% of patients, congenital esophageal atresia was a component of chromosomal aberrations and syndromes such as VACTERL association, Down's syndrome, Edward's syndrome and CHARGE syndrome. The etiology of EA/TEF is unknown. Many environmental factors, genetic disorders and chromosomal aberrations may possibly increase the rate of this disorder [10–12].

Surgical repair modified according to the type of atresia is a principal mode of treatment. In recent years, in some centers, surgical repair is conducted using the thoracoscopic technique [13–15]. The benefits of the thoracoscopic approach are well known and include cosmetic effects, avoidance of chest deformation and lessening of pain. It is unknown whether the change in surgical technique could possibly influence other complications such as an increased prevalence of gastroesophageal reflux disease. It is linked to disturbances of esophageal motor activity and its clearance as well as increased frequency of pathological esophageal reflux [16]. In the course of these disorders, the number of such complications as esophagitis, epithelial metaplasia, Barrett esophagus and the risk of neoplasm of the esophagus increases [17, 18]. In addition to these pathological complications, an esophageal stricture at the anastomosis site may appear.

Objectives

The goal of the study was to assess disease symptoms, physical development and gastroesophageal reflux disease symptom frequency in children who underwent thoracoscopic surgery of congenital esophageal atresia.

Material and Methods

The study comprised 22 children, aged 16 to 79 months (average age 47.3 months), treated in the first days of life with thoracoscopic surgery due to EA/TEF (type III). All children were operated on in the Department of Pediatric Surgery and Urology of Wroclaw Medical University. Among the patients there were 14 boys (63.6%) and 8 girls (36.4%). In 7 children (31.8%), EA/TEF coexisted with other congenital disorders such as atresia of the anus (3 children), retrosternal diaphragmatic hernia, kidney agenesis and congenital heart disorders. In a four-year-old girl, potential celiac disease was diagnosed. In two children, multiple esophageal dilatations were performed due to anastomosis strictures. In one child, Nissen fundoplication was performed. Four children had previously been treated with proton pump inhibitors. In 19 children (86.4%), 24-h intraluminal manometry with pH-metry was performed. The study was performed using disposable ComfortTec (Sandhil Scientific, Inc., Highlands Ranch, USA) MII/pH catheters, adjusted to age and height. The probe was equipped with 6 sensors of impedance distributed every 1.5 cm and a single pH sensor in the distal part of the esophagus. In three patients (13.6%), the study was not completed due to a lack of patient cooperation and technical difficulties with the catheter insertion. The following parameters of impedance were assessed: total number of reflux episodes, symptom index (correlation of symptoms with reflux episodes), reflux index (percentage of time of pH below 4.0), index of exposition for reflux content, average time of acid content clearance, average time of esophageal clearance after bolus passage and others. In 11 patients (50%), esophagogastroduodenoscopy was performed using Pentax EG-279K/2.8 with vision tract Pentax EPK-1000 under general anesthesia with samples collection from the esophagus, stomach and duodenum. Additionally, a retrospective analysis of the medical history was done, taking into account a questionnaire used in the clinic in patients with gastroesophageal reflux disease and a special questionnaire prepared for this study containing demographic data, birth history and the usage of inhibitors of hydrochloric acid secretion in the stomach as well as the necessity of dilatation of the esophagus after surgery. All patients underwent physical examination and anthropometric measurements and body composition using InBody J10 (Biospace, Seoul, Korea). Diagnosis of gastroesophageal reflux disease was established based on symptoms from the history and findings in the physical examination and the results of the 24-h pH-metry study. Depending on the result of the MII/pH study, the children were divided into two groups. Ten children

with gastroesophageal reflux disease were allotted to the first group and 9 with the diagnosis that they did not have gastroesophageal reflux to the second.

All of the results were analyzed statistically using Fisher or Student's t-test with STATISTICA PL 10 (Statsoft, San Francisco, USA). An independent samples t-test was used for comparison of the impedance parameters and a two-tailed z-test was used for comparison of proportions. All differences were regarded as statistically signifficant when p-value was smaller than 0.05. The approval of the Bioethics Committee of Wroclaw Medical University was obtained for the study (KB-197/2012).

Results

In Table 1, the symptoms observed in all children who underwent corrective surgery for esophageal atresia, both with and without gastroesophageal reflux disease (GERD), are presented. The frequent occurrence of dysphagia (45.4%), *fetor ex ore* (54.4%), belching (36.4%), cough (63.6%) and recurrent bronchitis is worth noting. The comparisons of the symptom rate in children with and without gastroesophageal reflux disease were statistically insignificant. Cough was the most frequently observed symptom.

The state of nutrition in the children was evaluated according to birth body mass and gestational age. Prematurity was present in half of the patients, including 40% with gastroesophageal reflux disease. Body mass was below the 3rd percentile in 27.3% of the patients. In 31.8%, body mass deficiency was observed (below the 10th percentile), which correlated with prematurity and in 27.3% with low birth body mass (below 2500 g) (Table 2). Short stature was demonstrated in 28.6% of the patients and malnutrition of various degrees also in 28.6%. A deficiency of both body mass and

Table 1. Comparison of clinical symptom frequency in children after repair surgery of congenital esophageal atresia

Symptoms	Studied children after repair surgery of esophageal atresia						
	total (n = 22)		MII/pH performed (19)				
			with GERD (10)		without GERD (9)		Fisher test p
	n	%	n	%	n	%	
Heartburn	3	13.6	3	30.0	0		0.210
Vomitus	7	31.8	4	40.0	2	22.2	0.628
Regurgitation	9	31.8	1	10.0	0		1.000
Belching	8	36.4	3	30.0	4	44.4	0.649
Fetor ex ore	12	54.5	7	70.0	4	44.4	0.369
Dysphagia	10	45.4	4	40.0	5	55.5	0.656
Cough	14	63.6	8	80.0	4	44.4	0.169
Recurrent bronchitis	11	50.0	6	60.0	4	44.4	0.656

Table 2. Prematurity and body mass in children with congenital esophageal atresia

	Prematurity	Body mass < 3 c	Body mass ≥ 3 c and ≤ 10 c	Body mass < = 10 c and prematurity	Body mass < = 10 c with birth body mass < 2500 g
Whole group (n = 22) (%)	10 45.45	6 27.3	2 9.1	7 31.8	6 27.3
With MII/pH performed (n = 19) (%)	7 36.8	4 21	3 15.8	5 26.3	4 21
With GERD (n = 10) (%)	4 40	2 20	1 10	2 20	1 10
Without GERD (n = 9) (%)	3 33.3	2 22.2	2 22.2	3 33.3	3 33.3

c = percentile.

Table 3. The parameter of 24-h MII/pH in children after repair of esophageal atresia

Parameter	Children after correction of esophageal atresia			
	total n = 19	**children with GERD n = 10**	**children without GERD n = 9**	**student's t-test p**
	mean ± SD (from–to)	**mean ± SD (from–to)**	**mean ± SD (from–to)**	
Total number of reflux episodes	62.9 ± 30.2 (10–165)	92.78 ± 41.49 (33–165)	37.10 ± 18.95 (10–72)	0.002
Symptom index	50.8 ± 28.2 (11–100)	60.40 ± 29.78 (11–100)	42.00 ± 26.75 (17–100)	0.176
Reflux index (RI) (percentage of recording time with pH < 4)	5.8 ± 3.7 (0–26.8)	10.67 ± 7.90 (0.3–26.8)	0.556 ± 0.93 (0–2.9)	0.001
Bolus exposure index (%)	4.7 ± 2.9 (0.7–13.2)	6.41 ± 3.97 (0.8–13.2)	2.8 ± 2.0 (0.7–5.6)	0.025
Mean time of esophageal acid exposure (min)	40.2 ± 41.3 (1.2–150.6)	66.56 ± 43.18 (22.9–150.6)	16.56 ± 21.47 (1.2–67.9)	0.006
Mean time of non-acid esophageal exposure (min)	19.2 ± 16.5 (0.6–52.7)	22.41 ± 19.45 (0.6–52.7)	16.26 ± 13.83 (0.8–50.4)	0.442
Mean time of esophageal exposure (min)	59.3 ± 45.8 (8.5–159.9)	88.82 ± 44.93 (2.8–159.9)	37.78 ± 27.49 (8.5–79.8)	0.009
Mean time of longest episode (min)	19.2 ± 26.6 (1.8–109.5)	27.67 ± 32.98 (3.8–109.5)	12.83 ± 18.78 (1.8–59.9)	0.251
Mean acid clearance time (s)	161.1 ± 117.5 (16–634)	259.5 ± 176.29 (41–634)	52.22 ± 59.04 (16–205)	0.003
Mean bolus clearance time (s)	14.8 ± 5.1 (7–24)	14.44 ± 5.81 (7–22)	15.20 ± 4.73 (10–24)	0.760

height was observed in 21.4% of the children studied. There were no differences in the composition of the body between the children studied and the general population of healthy children, however a tendency to greater muscle tissue percentage, as measured in the mid-arm, was observed. Based on clinical symptoms and the results of the MII/pH, gastroesophageal reflux disease was diagnosed in 10 children (52.6%), including pathological acid reflux in 9 children and a non-acid reflux in one child.

Analysis of the parameters of the MII/pH demonstrated an increased number of reflux incidences, increased symptom index, increased index of exposure to both acid and non-acid content, a longer persistence of bolus and worse clearance of the esophagus. Meticulous comparative analysis of 24-h MII/pH in children with and without GERD demonstrated significant difference in the total number of reflux episodes, reflux index, bolus exposure index, mean time of esophageal acid exposure, mean time of esophageal exposure, and mean acid clearance time (Table 3).

An endoscopic analysis of the upper part of the gastrointestinal tract performed in 11 children (50%) demonstrated a significant narrowing of the esophagus in two of them (18%). In four patients (36.4%), esophagitis was diagnosed (grade A, according to the Los Angeles classification), confirmed by histopathological studies, and in one child (9.1%), gastric metaplasia was present. In four children, chronic gastritis was diagnosed (corpus and the prepyloric part), and *H. pylori* infection in one patient, confirmed by the urease test. The examination of mucosa samples from the duodenum did not demonstrate atrophy of the villi in the duodenum (Marsh scale – 0).

Discussion

EA/TEF is a severe congenital disorder of the intestinal tract requiring corrective surgery in the first days of life. This disorder is frequently accompanied by other congenital disorders such as anal atresia, kidney agenesis, heart disorders and many

other. In the studied group of children, these disorders were present in 7 out of 22 children (31.8%), which is in accordance with other studies [10]. In our analysis, 10 children with EA/TEF (45.5%) were born prematurely with low body mass and the rate of prematurity was high but similar to other studies [10]. However, it surpassed the norm for the general population, since in Poland in 2008 the rate of premature births was 6.96% [19]. In our studies, body mass deficiency correlated with prematurity in 31.8% of children and in 28.6% short stature and low body mass were observed. Body composition of our group was better than in the general population, which may reflect good protein nutrition. In most of the children after reconstructive surgery due to EA/TEF, symptoms in the esophagogastrointestinal tract and respiratory system were observed. The most frequently observed symptoms were cough and recurrent bronchitis and heartburn in children with gastroesophageal disease, but their occurrence was statistically insignificant. The remaining symptoms were observed in children both with and without gastroesophageal reflux disease.

In our study, the prevalence of gastroesophageal reflux disease was high – 52.6%. The values of reflux index, time of content remaining in the esophagus, including acid content, and time of esophageal clearance of acidic content were statistically higher in children with diagnosed gastroesophageal reflux disease than in children without this disease. Our results were similar to those from other studies [16, 20, 21]. Di Pace et al. [21], using MII/pH, demonstrated that in children who underwent a corrective operation for EA/TEF, gastroesophageal reflux disease was frequent and that the time of bolus clearance, acid clearance and time of bolus passage were pathological. Catalano et al. [22] demonstrated a correlation of gastroesophageal reflux disease with non-acid reflux. This phenomenon may be related to the frequent usage of proton pump inhibitors in the children before the MII/pH study. The patients in our study had not been receiving those drugs for several weeks before examination. The disturbances in children operated on due to EA/TEF described above are at risk for serious complications. According to van Wijk et al. [23], transient lower esophageal sphincter relaxation was the most common mechanism underlying gastroesophageal reflux disease in infants, delayed bolus clearance and delayed gastric emptying. Besides esophagitis, Barrett esophagus and adenocarcinoma may also develop [17, 24, 25]. In our study, in one child, gastric metaplasia was present in the lower part of the esophagus. According to Burjonrappa et al. [26], metaplasia occurs in about 15% of patients and the average time to its occurrence was about 10 years. Endoscopic examinations are best suited to detect changes of this type, therefore children who underwent corrective surgery of esophageal atresia require monitoring and check-up examinations and treatment if necessary. It seems that thoracoscopic repair of AE/TEF did not influence the problems with GERD in any way, but this requires more comparative studies.

In summary, it can be stated that, in children who underwent corrective surgery of esophageal congenital atresia, gastroesophageal reflux disease, as well as other complications such as esophagitis, stricture, metaplasia and Barrett esophagus, are frequently observed. These changes are caused by disturbances of the esophagus and lower esophageal motility. Children after surgery require constant monitoring and treatment of complications in order to prevent serious, life-threatening complications in later years. It seems that thoracoscopic repair of AE/TEF did not influence in any way the problems with GERD, but this requires more comparative studies.

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