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ORIGINAL ARTICLE

Gastroesophageal reflux in patients treated for congenital diaphragmatic hernia: short- and long-term evaluation with multichannel intraluminal impedance

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Abstract
Purpose The incidence of GER, related symptoms and complications in patients treated for congenital diaphragmatic hernia (CDH) are poorly defined. The aim was to evaluate incidence and development of GER in children treated for CDH in a short- and long-term follow-up period, identifying potential risk factors of morbidity.
Methods Thirty-six patients were evaluated with pH-MII at a median age of 6 months (T1) and re-evaluated with pH-MII and endoscopy at a median age of 5 years (T2).
Results The incidence of reflux was 83 % in T1 and 61 % in T2; the incidence of symptoms was 62 % in T1 and 38 % in T2. In both groups the reflux was mainly non-acidic. Patch, intrathoracic stomach and esophageal dysmotility were risk factors for GER.
Conclusions The incidence of GER and symptoms decrease over the time but it was higher than in the literature, probably because it is mainly non-acidic and evaluable only with MII. The esophageal dysmotility was found to be the main risk factor. An high incidence of reflux and esophagitis was found also in asymptomatic patients, and so a close follow-up is recommended in all patients even if it is asymptomatic.

Keywords Congenital diaphragmatic hernia · Gastroesophageal reflux disease · Esophageal dysmotility · Multichannel intraluminal impedance · Endoscopic esophagitis

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Introduction

Congenital diaphragmatic hernia (CDH) is a life-threatening congenital anomaly, occurring in 1 on 2,500 live births approximately. Despite advances in antenatal diagnosis and postnatal management, mortality rate remains elevated. Traditionally, most attention has been focused on therapies that reduce perinatal and neonatal mortality, whereas few studies have focused on chronic morbidity and long-term outcome. In fact, follow-up of infants treated for CDH shows many complications [1].

Gastroesophageal reflux (GER) is one of the major sequelae in infants who survive congenital diaphragmatic hernia repair. The causal linkage between CDH and GER remains unclarified and several possibilities have been suggested. Stolar et al. [2] described a foregut dysmotility probably related to the translocation of the stomach into the chest, with kinking and obstruction of the gastroesophageal junction. High incidence of non-acidic GER and impaired esophageal motility that involve distal esophagus have

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been previously reported in our other study in patients with CDH: a more impaired esophageal motility is closely related to more altered GER parameters [3]. GER seems to depend on the size of the defect and also, use of patch in large CDH can be considered a risk factor for GER [4]. However, several authors suggested that the diaphragmatic patch may lower the tension on the crura and then protect from GER onset [5]. The real incidence of GER, related symptoms and complications in children treated for CDH are still poorly defined.

Multichannel intraluminal impedance (MII) has recently been added to the repertoire of tests available to study both gastroesophageal reflux and esophageal motility in pediatric patients [6–10].

The aim of this study was to assess with pH-MII the incidence and the development of GER, GER-related symptoms and GER complications, in a population of children treated for CDH in a short- and long-term follow-up period, identifying potential risk factors of morbidity.

Materials and methods

Patients

Thirty-six patients (22 females and 14 males), who underwent surgical repair for CDH between 2004 and 2007, were included in the study. All patients were evaluated clinically and studied with 24 h pH-Multichannel Intraluminal Impedance (pH-MII) at a median age of 6 months (range 4–8 months), to estimate the short-term incidence of symptoms and GER (T1 group); all patients were re-evaluated at a median age of 5 years (range 36–84 months) with pH-MII and esophageal endoscopy, to study the esophageal motility, the long-term incidence of symptoms, GER and esophagitis (T2 group). Symptoms and thoracic deformities were appraised during the clinical examination. Chest X-ray was performed at 6 months and 5 year of age in all patients to rule out hernia recurrence [11]. We excluded the patients who did not complete the follow-up from the study.

All patients had a left-sided diaphragmatic defect and were operated on with a left subcostal laparotomy. Twelve patients (33 %) received a diaphragmatic patch (Goretex), because of the big size of the defect. In 6/24 patients, who had primary closure, the suture of the diaphragmatic defect was performed under mild tension. In 26 patients (72 %) an intrathoracic stomach was found at the time of surgery. All patients requiring patch showed the intrathoracic herniation of the stomach, except one patient affected by a large isolated lateral defect only with involvement of the small bowel and spleen.

No patient required preoperative extracorporeal membrane oxygenation (ECMO). No patient had other major anomalies and underwent antireflux surgery at the time of the first evaluation (T1). All children were admitted to our Unit on the day of the procedure and discharged the following day. No patient was taking medications influencing esophageal motor function or acidic secretion at the time of the evaluation. Parents were asked to sign an informed consent before every procedure and regarding the inclusion in the study; details that might disclose the identity of the subjects under study were omitted.

Procedure

All patients underwent 24 h combined esophageal pH/MII monitoring, using hardware and software by Sandhill Technologies (Sandhill Scientific). The procedure was performed with age-appropriate probes with six impedance channels. Parents were asked to fill a diary during the procedure to record the exact time of every meal, body position and symptoms. In T2 group; before removing the probe, when the patients were calmer and collaborating, motility analysis was performed. In the orthostatic position, children were given ten swallows of 5 mL of normal saline (standardized impedance value) each 20–30 s apart. The tracings were revised visually and manually for reflux and motility parameters as previously described [3]. We analysed reflux parameters: number of reflux episode, both acid and non-acid, and their height, number of pH only reflux and re-reflux, number of long reflux (>3 min), the Bolus Exposure Index (BEI) as main reflux index because is independently from pH, the reflux index (RI) as acid exposure index, the activity of acid and bolus clearance (MACT and MBCT respectively). As motility parameters we analysed the following: bolus presence time for every channel (BPT) and total and segmental transit time (TBTT and STT respectively).

Statistical analysis

Statistical analysis of quantitative and qualitative data, descriptive statistics included, was performed for all the items. Continuous data were expressed as mean ± standard deviation, unless otherwise specified.

Frequency analysis was performed with Chi square test to evaluate differences between patients with and without patch and with McNemar statistic test to compare the variables between T1 and T2 groups.

The paired Wilcoxon signed-rank test and the paired samples Student's *t* test were used to compare between T1 and T2 groups the non-parametric and parametric variables, respectively.

The one-way analysis of variance (ANOVA) was performed to evaluate mean differences between patients with and without patch.

All p values were two-sided and p values <0.05 were considered statistically significant.

Data were analysed by the Epi Info software (version 6.0, CDC, Atlanta, GA, US) and the SPSS Software 14.0 version (SPSS, Inc.,Chicago, Ill, US).

Results

The correlation between clinical parameters and GER was described in Table 1.

In the T1 group (short term evaluation) GER was observed in 83 % (30/36) of patients, with an high prevalence of non-acidic refluxes (80 %). Overall, of 30 patients with GER, 66 % reported symptoms, 34 % have patch and 80 % had an intrathoracic stomach. Of all patients with patch, 83 % showed GER which was symptomatic in 67 %. Of all patients with intrathoracic stomach, 93 % showed GER which was symptomatic in 66 %. Symptoms (recurrent vomiting and chronic cough) were reported by 62 % of patients. Of symptomatic patients, 91 % showed GER, whereas 9 % reported cough not related to GER; of asymptomatic patients, 72 % showed GER.

In the T2 group (long term evaluation) the incidence of GER was 61 % (22/36 pts) with a preponderance of non-acidic reflux (60 %). Overall, of 22 patients with GER, 54 % reported symptoms, 45 % have patch and 82 % had intrathoracic stomach. Of all patients with patch, 50 % showed GER and they are all symptomatic. Of all patients with intrathoracic stomach, 69 % showed GER, 55 % of which symptomatic. Symptoms (epigastric pain, chronic cough, recurrent bronchitis) were reported by 38 % of patients; 86 % of symptomatic patients showed GER, whereas 2 patients reported cough not related to GER; 45 % of asymptomatic patients showed GER.

Impedance parameters were described in Table 2: no statistically significant differences between the two groups were found, except for number and height of non-acidic reflux. The GER parameters were related to the patch in Table 3: patients with patch showed parameters of reflux more altered than patients without patch in both group. Regarding the motility analysis in T2 group, parameters of esophageal motility resulted more altered than values reported in healthy children [9] with more prolonged total and segmental transit time (Table 4). The Bolus Exposure Index (BEI) was related to the presence of patch, esophagitis and transit time: higher values of BEI were found in patients with esophagitis, patch and a more prolonged transit time (Table 5).

In both groups more than 80 % of reflux episode were short (<3 min) and occurred in the postprandial period.

In T2 group esophagitis was found in 36 % of patients with GER: the 50 % of these patients were asymptomatic and without patch. The 50 % of these patients was submitted on antireflux surgery, whereas the other patients responded to medical treatment.

Thoracic deformities were recorded in 16 % of patients; all these patients underwent closure of the diaphragmatic defect under tension without patch and developed a severe GER.

Recurrence of diaphragmatic hernia was observed in 5 % of patients in T2 group and they subjected to a second surgical procedure. No recurrence of hernia was found in T1 group.

Table 1 Compared results between the two groups: correlation between clinical parameters and GER

	T1 Group % (no. of patients)	T2 Group % (no. of patients)
Patients GER+	83 (30/36)	61 (22/36)*
Symptomatic	66	54
Asymptomatic	34	46*
Patch+	34	45*
Intrathoracic stomach+	80	82
Patients with patch	33 (12/36)	33 (12/36)
GER+	83	50*
GER + symptomatic	67	100*
Patients with intrathoracic stomach	72 (26/36)	72 (26/36)
GER+	93	69*
GER + symptomatic	66	55
Symptomatic patients	62 (22/36)	38 (14/36)*
GER+	91	86
GER−	9	14
Asymptomatic patients	38 (14/36)	62 (22/36)*
GER+	72	45*
GER−	28	55*

Legend of symptoms: T1 group: recurrent vomiting and chronic cough. T2 group: epigastric pain, chronic cough and recurrent bronchitis

No. number, *GER* gastroesophageal reflux

* $p < 0.05$

Table 2 Impedance parameters in the two groups

Impedance parameters	T1 Group (mean ± SD)	T2 Group (mean ± SD)	*p*
Incidence of GER (%)	83.3	61.1	0.528
No. of tot of GER	71.7 ± 33.2	60.6 ± 44.5	0.191
No. of acidic GER	21.1 ± 25.5	21.1 ± 30.9	0.99
No. of non-acidic GER	50.6 ± 31.7	39.9 ± 34.0	0.031
No. of high non-acidic GER	17.7 ± 12.8	8.61 ± 15.2	0.006
No. of high acidic GER	9.7 ± 16.7	18.6 ± 29.0	0.22
No. of pH only reflux	2.89 ± 4.2	2.89 ± 4.7	1.00
No. of re-reflux	2.1 ± 3.4	1.8 ± 3.5	0.651
BEI (%)	4.2 ± 1.9	3.6 ± 2.4	0.246
RI (%)	4.8 ± 5.0	4.5 ± 6.0	0.864
MACT (s)	106.0 ± 59.5	118.0 ± 86.9	0.565
MBCT (s)	45.2 ± 21.4	47.8 ± 32.8	0.735

No. number, *tot* total, *GER* gastroesophageal reflux, *BEI* Bolus Exposure Index, *RI* reflux index, *MACT* mean acid clearance time, *MBCT* mean bolus clearance time

Discussion

Gastroesophageal reflux (GER) is common after congenital diaphragmatic hernia repair.

The incidence of GER varies according to used diagnostic criteria: symptoms, radiologic findings, pH-metry or endoscopy. It may occur in 30–70 % of patients [12, 13], but an incidence of up to 80 % has been reported in patients treated with ECMO before CDH repair [14]. It is also reported that 15–70 % of CDH patients remains symptomatic under medical treatment, and thus requires fundoplication [14–16]. The incidence and the severity of GER symptoms, however, decrease after the first year of life [12]. GER is an important parameter of overall short- and long-term morbidity even if the mechanism responsible, either intrinsic or extrinsic, is still unclear [17–19]. On endoscopy an alarming finding, such as Barrett's esophagus, was observed and recently CDH survivors with esophageal adenocarcinoma have been described [20]. For these reasons patients with CDH require a close surveillance.

Our study assesses the incidence and pattern of GER using pH-MI in a population of children treated for CDH at birth, evaluated at 6 months and 5 years of age; the analysis of the same patients over the time implies a high statistical significance of the obtained results. We also evaluated the correlation between GER and esophageal motility, in addition to the main risk factors as described in the literature (patch repair and intrathoracic stomach). Moreover, complications such as esophagitis, thoracic deformities and hernia recurrence were estimated.

Our results confirm that, even in patients with CDH, the incidence of GER decreases over the time, varying from 83 % in the T1 group to 61 % in the T2 group, however, remaining elevated. The incidence of GER reported in this series, as in our previous studies, resulted higher than that reported in the literature [12, 13]; this may probably due to the high incidence of non-acidic reflux, which is not detectable using conventional pH-metry. No differences were found considering reflux parameters in the two groups except for number of non-acidic reflux (Table 2); this means that the severity of reflux does not change over the time because only this value does not seem sufficient to influence the severity of reflux. Interestingly, high incidence of GER was found also in asymptomatic patients in both groups (72 and 45 % in T1 and T2 groups, respectively); furthermore, among patients with GER, the incidence of asymptomatic cases increased in T2 group (34 vs 46 %) (Table 1).

Koivusalo described a positive development of symptoms [12] and the same was also noted in our series: 45 % of symptomatic patients of T1 group healed, whereas 55 % remained symptomatic at the second evaluation (T2 group); however, 14 % of patients who were asymptomatic in T1 evaluation became symptomatic in T2. As for the evolution of GER, 33 % of patients healed in T2 evaluation, whereas 67 % continued to have GER.

A detailed statistical analysis was conducted about the relationship between the use of patch and GER. Patients with patch reported a more altered reflux parameters if compared with patients without patch; no statistically significant differences were found between patients with and without patch regarding to the incidence of reflux. Hence, it is likely that the presence of patch influences the severity of reflux without affecting its incidence and that the severity of reflux does not change over the time. The percentage of patients with patch who develop GER decreased during years (83 vs 50 % in T1 and T2 groups, respectively); however, among patients with GER, the percentage of

Table 3 Impedance parameters in the two groups with analysis regarding patch

Impedance parameters	T1 Group (mean ± SD)	T2 Group (mean ± SD)	*p* T1 vs T2
No. of tot of GER			
Patch +	87.5 ± 40.7*	73.8 ± 61.2*	0.477
Patch −	63.9 ± 27.4	54.0 ± 34.8	0.301
No. of acidic GER			
Patch +	42.3 ± 36.9*	24.5 ± 38.6	0.28
Patch −	10.5 ± 4.5	19.5 ± 28.2	0.306
No. of non-acidic GER			
Patch +	45.1 ± 44.4	49.3 ± 45.5	0.426
Patch −	53.4 ± 25.1	34.4 ± 27.6	0.006
No. of high non-acidic GER			
Patch +	17.0 ± 18.4	17.0 ± 24.5*	1.000
Patch −	18.0 ± 9.9	4.4 ± 5.4	0.001
No. of high acidic GER			
Patch +	22.5 ± 25.3*	21.8 ± 38.3	0.28
Patch −	3.4 ± 2.7	17.0 ± 25.0	0.07
No. of pH only reflux			
Patch +	6.1 ± 6.1*	4.8 ± 7.5	0.601
Patch −	1.25 ± 1.2	1.92 ± 2.2	0.388
No. of re-reflux			
Patch +	4.67 ± 5.1*	3.3 ± 5.7	0.505
Patch −	0.92 ± 1.1	1.08 ± 1.5	0.787
BEI (%)			
Patch+	5.4 ± 2.3*	4.3 ± 3.3	0.306
Patch−	3.6 ± 1.4	3.2 ± 1.9	0.576
RI (%)			
Patch+	8.9 ± 7.2*	5.1 ± 7.3	0.270
Patch−	2.7 ± 1.2	4.2 ± 5.6	0.410
MACT (s)			
Patch+	153.1 ± 82.9*	135.8 ± 120.1	0.688
Patch−	82.4 ± 22.9	109.1 ± 69.8	0.274
MBCT (s)			
Patch+	46.8 ± 23.7	51.1 ± 36.8	0.681
Patch−	44.4 ± 21.3	46.2 ± 32.2	0.868

No. number, *tot* total, *GER* gastroesophageal reflux, *BEI* Bolus Exposure Index, *RI* reflux index; *MACT* mean acid clearance time, *MBCT* mean bolus clearance time

* $p < 0.05$ patch+ vs patch–

those with patch increased in the T2 group (33 vs 45 %). Most of the patients with patch were asymptomatic in both groups; however, patients with patch had higher incidence of symptoms if compared with patients without patch.

On the basis of our results, we can confirm that patch is a risk factor for severe GER (more altered impedance parameters) and it influences the onset of symptoms, as recently described [21, 22]. Also the closure of the diaphragm under tension is a risk factor for severe GER, as previously reported by some Authors who consider that the use of a prosthetic patch, during diaphragmatic hernia repair, could reduce the morbidity related to GER lowering the strain on the crura [5]. In our series, diaphragmatic defect closure under mild tension and without patch was observed in all patients with thoracic deformities (16 %) and all these patients had GER.

However, our series is too small to draw definitive conclusions about patch, even because the number of patients with and without patch is different.

A more severely impaired esophageal motility was observed in patients with patch, probably due to the wider size of the diaphragmatic defect and the greater compression

Table 4 Motility parameters in T2 Group

Motility parameters (s)	Mean (±SD) (range)
SST1	2.0 (0.7) (0.6–3.5)
SST2	2.1 (0.7) (0.7–3.4)
STT3	2.4 (0.6) (0.8–3.6)
STT4	2.7 (0.7) (1.0–3.8)
STT5	3.2 (0.7) (1.4–4.0)
BPT1	4.9 (2.6) (1.5–9.2)
BPT2	5.2 (2.7) (1.3–9.3)
BPT3	6.0 (2.6) (1.9–9.5)
BPT4	6.4 (2.7) (1.7–9.7)
BPT5	7.4 (2.4) (3.3–10.2)
BPT6	8.4 (2.5) (3.6–10.7)
TBTT	9.7 (2.3) (5.6–14.2)

Mean values calculated on 10 standard swallows for all patients

STT segmental transit time, *BPT* bolus presence time, *TBTT* total bolus transit time

Table 5 Correlation of BEI (impedance reflux parameter), TBTT (impedance motility parameter), presence of patch and esophagitis in randomly chosen patients of T2 group

Patient no.	Patch	Esophagitis	BEI (%)	TBTT (s)
29	+	+	8.1	14.25
17	+	+	7.2	13.83
4	+	+	6.9	13.45
12	+	+	6.8	11.6
32	−	+	4.9	10.04
9	+	+	4.8	9.98
30	−	+	3.6	8.96
25	−	−	1.3	6.14
13	−	−	0.9	6.12
2	−	−	1.2	6.3
35	−	−	0.7	5.6

BEI Bolus Exposure Index (normal < 1.4 %), *TBTT* total bolus transit time (normal values < 8.3 s in healthy children from J Ped Surg 2011;46:1881–1886)

on the fetal esophagus, which may impair the intrinsic innervation of the esophagus [2, 3, 19].

The esophageal dysmotility was found to be the main risk factor for the presence, the severity and the maintenance of reflux over the time. A correlation between BEI and bolus transit time was found (Table 5): patients with more prolonged esophageal transit time showed more pathologic exposure bolus. Probably an impaired esophageal motility influences the clearing and then the bolus exposure; a more altered Bolus Exposure Index indicates a pathological reflux with risk of the persistence over the time and of esophagitis. Patients without impaired motility have a GER without complications and may recover.

Among the patients with GER, 36 % showed esophagitis on endoscopic evaluation; 50 % of these patients had patch and they were asymptomatic. All patients with esophagitis had more altered parameters of esophageal motility than patients without esophagitis (Table 5).

The intrathoracic stomach was confirmed to be a risk factor for GER, probably causing an alteration of gastro-esophageal junction.

The incidence of recurrence in our study is very low compared to data reported in literature [21–24], probably due to the little use of patch and the accurate closure of defect.

As for the length of follow-up in our series, we are aware that 5 years are a mild term period, but pH-MII is a recent technique and so the mean time of follow-up is conditioned from this; further studies are necessary over the time to establish the real long-term follow-up in these patients using pH-MII.

In our previously published study [3], we analysed patients with a median age of 5 years to identify for the first time an esophageal dysmotility as yet evaluated in patients with esophageal atresia. In this study, the objective was different: we wanted to study the reflux and its evolution over time, and so we reported the previous data comparing them with those obtained at 6 months.

In conclusion, our results about the incidence and evolution of GER suggest that a close clinical and instrumental monitoring of patients treated for CDH is mandatory, even in asymptomatic patients. The pH-MII is a gold standard technique for the evaluation of patients with esophageal and gastric malformations, because it analyses the real incidence of GER (both acid and non-acidic) and esophageal motility, identifying patients with severe GER and dysmotility at higher risk of complications. The incidence of complications as esophagitis does not justify antireflux preventive surgery; in this study only medical treatment and a close clinical and instrumental monitoring seem to be sufficient to avoid complications in the most of cases. Besides, we believe that CDH patients, as those treated at birth for esophageal atresia, should start antireflux medications (antiacidic and prokinetic therapy) early in the postoperative period and not only after the onset of GER symptoms. Uunfortunately, the currently available prokinetic medications have only modest efficacy in relieving reflux symptoms, and the side effect profile of these agents renders them a less useful clinical practice [25]. However, we agree with some authors regarding the association between PPI and prokinetic to improve the PPI effect [26].

In these children pH-MII shows that most refluxes are non-acidic, short and mainly postprandial refluxes. We can, therefore, suppose that the relaxation of the lower esophageal sphincter is the main event for the occurrence of reflux and, therefore, the role of gastroesophageal junction

is essential [28, 29]. For these reason, meticulous attention to the diaphragmatic crura during surgical repair is highly recommended to minimize the risk of GER in CDH patients. We recommend fundoplication about the IPEG guidelines [27], although the long-term success rate of this procedure in CDH patients has not to be proven.

Conflict of interest No competing financial interests exist. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Peetsold MG, Heij H, Kneepkens CMF et al (2009) The long term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. Ped Surg Int 25:1–17
2. Stolar JH, Levy JP, Dillon PW et al (1990) Anatomic and functional abnormalities of the esophagus in infants surviving congenital diaphragmatic hernia. Am J Surg 159:204–207
3. Di Pace MR, Caruso AM, Farina F et al (2011) Evaluation of oesophageal motility and reflux in children treated for congenital diaphragmatic hernia with the use of combined multichannel intraluminal impedance and pH monitoring. J Pediatr Surg 46:1881–1886
4. Su W, Berry M, Puligandla PS et al (2007) Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. J Pediatr Surg 42:1639–1643
5. Kieffer J, Sapin E, Berg A et al (1995) Gastroesophageal reflux after repair of congenital diaphragmatic hernia. J Pediatr Surg 30(9):1330–1333
6. Mattioli G, Pini-Prato A, Gentilini V et al (2006) Esophageal Impedance/pH Monitoring in pediatric patients: preliminary experience with 50 cases. Dig Dis Sci 51:2341–2347
7. Van Wijk MP, Benninga MA, Omari T et al (2008) Role of the multichannel intraluminal impedance technique in infants and children. J Pediatr Gastroenterol Nutr 48:2–12
8. Woodley FW, Mousa H (2006) Acid gastroesophageal reflux reports in infants: a comparison of esophageal pH monitoring and multichannel intraluminal impedance measurements. Dig Dis Sci 51:1910–1916
9. Di Pace MR, Caruso AM, Catalano P et al (2011) Evaluation of esophageal motility using multichannel intraluminal impedance in healthy children and with gastroesophageal reflux. J Pediatr Gastroenterol Nutr 52(1):26–30
10. Di Pace MR, Caruso AM, Catalano P et al (2011) Evaluation of oesophageal motility and reflux in children treated for esophageal Atresia with the use of combined Multichannel Intraluminal Impedance and pH monitoring. J Pediatr Surg 46:443–451
11. Rocha GM, Bianchi RF, Azevedo I et al (2008) Congenital diaphragmatic hernia. The post neonatal period. Eur J Pediatr Surg 18:307–312
12. Koivusalo A, Pakarinen MP, Lindahl HG et al (2008) The cumulative incidence of significant gastroesophageal reflux in patients with congenital diaphragmatic hernia- systematic clinical, pH metric and endoscopic follow-up study. J Pediatr Surg 43:279–282
13. Jaillard SM, Pierrat V, Dubois A et al (2003) Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. Ann Thorac Surg 75:250–256
14. Fashing G, Huber A, Uray E et al (2000) Gastroesophageal reflux and diaphragmatic motility after repair of congenital diaphragmatic hernia. Eur J Pediatr Surg 10(6):360–364
15. Chamond C, Morineau M, Gouizi G et al (2008) Preventive antireflux surgery in patients with congenital diaphragmatic hernia. Worl J Surg 32:2454–2458
16. Guner YS, Elliot S, Marr CC et al (2009) Anterior fundoplication at the time of congenital diaphragmatic hernia repair. Pediatr Surg Int 25:715–718
17. Qi B, Soto C, Diez-Pardo JA et al (1997) An experimental study on the pathogenesis of gastroesophageal reflux after repair of diaphragmatic hernia. J Pediatr Surg 32(9):1310–1313
18. Arena F, Romeo C, Baldari S et al (2008) Gastrointestinal sequelae in survivors of congenital diaphragmatic hernia. Pediatr Int 50:76–80
19. Pederiva S, Rodriguez J, Tovar J (2009) Abnormal intrinsic esophageal innervation in congenital diaphragmatic hernia: a likely cause of motor dysfunction. J Pediatr Surg 44:406–409
20. Steven MJ, Fyfe AH, Raine PA et al (2007) Esophageal adenocarcinoma:a long term complication of congenital diaphragmatic hernia. J Pediatr Surg 42:E1–E3
21. Valfrè L, Braguglia A, Conforti A et al (2011) Long term follow-up in high risk congenital diaphragmatic hernia survivors: patching the diaphragm affects the outcome. J Pediatr Surg 46: 52–56
22. Peetsold MG, Kneepkens CM, Heij HA et al (2010) Congenital diaphragmatic hernia: long term risk of gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 51(4):448–453
23. Laituri CA, Garey CL, Valusek PA et al (2010) Outcome of congenital diaphragmatic hernia repair depending on patch type. Eur J Pediatr Surg 20:363–365
24. Jancelewicz T, Vu LT, Keller RL et al (2010) Long term surgical outcomes in congenital diaphragmatic hernia: observations from a single institution. J Pediatr Surg 45:155–160
25. Ramirez B, Richter JE (1993) Review article: promotility drugs in the treatment of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 7(1):5–20
26. Ndraha S (2011) Combination of PPI with a prokinetic drug in gastroesophageal reflux disease. Acta Med Indones Indones J Intern Med 43:233–236
27. IPEG Guidelines for the Surgical Treatment of PediatricGastroesophageal Reflux Disease (GERD) (2008) J Laparoendosc Adv Surg Tech 18(6). doi:10.1089/ lap.2008.9988
28. Dent J (2008) Pathogenesis of gastro-oesophageal reflux disease and novel options for its therapy. Neurogastroenterol Motil 20(51):91–102
29. Costa J, Campos M, Amil Dias J et al (2001) Delayed gastric emptying and gastroesophageal reflux: a pathophysiological relationship. J Pediatr Gastroenterol Nutr 32:471–474