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Source / Izvornik: **Pedijatrija danas, 2010, 6, 45 - 52**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:950304

GASTROESOPHAGEAL REFLUX AND GASTRIC HYPERACIDITY IN CYSTIC FIBROSIS PATIENTS

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Objective Gastroesophageal reflux (GER) is increased in children with cystic fibrosis (CF). The role of gastric hyperacidity, which is common in CF patients with GER is not well characterized.
Patients and Methods Twenty-five CF children underwent 24 hour oesophageal pH monitoring. From each pH monitoring diurnal and nocturnal intervals were selected. In 10 patients 24-hour simultaneous oesophageal and gastric pH monitoring were performed.
Results Thirteen of the 25 patients showed pathological GER. There were significantly more refluxes during diurnal pH monitoring. Nocturnal pH monitoring yielded significantly more refluxes longer than 5 minutes, longer episodes of refluxes and lower mean gastric and oesophageal pH.
Conclusion The method of choice for the diagnosis of gastroesophageal reflux in CF patients should be simultaneous oesophageal and gastric 24-hour monitoring including alert and sleep periods. Gastric acidity and reduced lung function facilitates reflux, which in turn might contribute to progression of pulmonary diseases as was seen in our patients.

Key words: Cystic fibrosis ▪ Gastroesophageal reflux ▪ Gastric hyperacidity ▪ Children ▪ Lung function ▪ pH monitoring

Introduction

Although great advances have been made in understanding genetic defects in CF, many aspects of gastrointestinal function in CF patients are still poorly understood (1, 2). CF patients have a high incidence of GER symptoms with demonstrable episodes of oesophageal acidification. However, the relationship between GER and lung complications in CF patients is not well understood. The reported incidence of GER in CF patients is

Received: July 29, 2009
Accepted: November 18, 2009

Pedijatrija danas 2010;6(1):45-52

between 25% and 100% (3-12). Several authors suggest that in all CF patients GER should be properly investigated through a complete medical interview and appropriate diagnostics tests, such as prolonged intraoesophageal pH monitoring (3, 4). The role of gastric hyperacidity in CF patients with GER has only been identified in a few articles (3, 13).

Although transient inappropriate lower oesophageal sphincter relaxation is the predominant reflux mechanism in these patients, the role of gastric hyperacidity, which is common in CF, is not well understood (3, 4, 13). The results of many studies indicate that basal and stimulated gastric acid secretion is greater in CF patients than in normal subjects (13, 14). However, there are some studies where no significant difference was found (15, 16).

The aim of this study was to establish the frequency of pathological GER in children with CF. The association between gastroesophageal reflux and gastric hyperacidity in children with cystic fibrosis has also been investigated.

Patients and methods

This was a prospective study of 25 children with CF who underwent 24 - hour oesophageal pH monitoring after informed consent from their parents had been obtained. Their clinical characteristics are shown in Table 1.

In the majority of patients the disease was diagnosed in infancy using a sweat test (cut-off limit was 60 mEq/L of sweat chloride) and genetic analysis.

In all children 24-hour oesophageal pH monitoring was performed. The monocrystaline antimony pH electrodes were calibrated using the Synetics pH 1.07 and 7.01 buffer solutions, respectively. X-ray controlled the length of insertion of the electrode. The probe was connected to a Mark III Digitrapper (Synetics Medical, Stocholm, Sweden). The children were permitted to move around freely and received their usual diet, except for cold and acidic liquids. The nurse-parent team kept a detailed hand-written diary. The data were analysed using the EsopHogram software program. An episode of acid reflux was defined as an abrupt fall in intraoesophageal pH less than 4 for at least 15 seconds. The standard variables were used including the reflux index (percentage of time when pH was less than 4), the number of reflux episodes and the number of reflux episodes longer than 5 minutes. According to Vandenplas and al. (17, 18) we considered a reflux index (RI) of >10% in patients younger than 1 year of age to be pathological, whereas a RI of > 5% was considered pathological in other age groups. The same limits were used in other articles (19, 20, 21, 22). Each 24-hour oesophageal pH monitoring was divided into diurnal (from 7 am to 7 pm) and nocturnal intervals. In 10 children 24 - hour simultaneous oesophageal and gastric pH monitoring was performed. In these patients we also measured gastric pH after fasting and immediately after a meal. The fasting period was determined as one hour prior to the next feeding. Furthermore, recordings of forced expiratory volume in the 1st sec (FEV1) were performed only in school age children with a dry sealed spirometer (Vicatest P2, Mijnhardts, Netherlands). FEV1 (% of predicted) was used as an indicator of pulmonary function and was measured a day before simultaneous oesophageal and gastric pH monitoring in 7 patients.

All data were tabulated using standard descriptive statistics. The Spearman rank correlation test was used to evaluate the severity of GER in relation to age and to gastric hyperacidity. Paired t-test was performed to detect significant ($p < 0.05$) differences of diurnal and nocturnal oesophageal and gastric pH monitoring in each patient.

Results

The planned 24-hour pH monitoring was successfully performed in all patients. Thirteen

Table 1 *Clinical features of patients with cystic fibrosis*
Tabela 1 *Kliničke karakteristike pacijenata sa cističnom fibrozom*

Variables/Varijable	$\bar{\chi}$	SD	Minimum/ Minimum	Maximum/ Maksimum
Age/Dob (Years/Godine) (n=25)	8.1	5.6	0.25	18
Boys/Dječaci (n=17)	-	-	-	-
Height/Visina (cm) (n=25)	122.9	34.8	52	172
Percentiles/Percentili (< 5)	-	-	-	-
Weight/Težina (kg) (n=25)	25.1	15.0	3.6	56
Percentiles/Percentili (< 5) (n=9)	-	-	-	-
[1]BMI/ITM (kg/m2) (n=25)	15.4	2.2	12.5	19
Percentiles/Percentili (< 5) (n=11)	-	-	-	-
Age of diagnosis (Month)/Dob kada je dijagnoza utvrđena (Mjeseci) (n=25)	21	32.7	1	110
< 1 Year/Godina (n=16)	-	-	-	-
2-6 Years/Godina (n=7)	-	-	-	-
> 7 Years/Godina (n=2)	-	-	-	-
Genotype/Genotip (n=25)	-	-	-	-
DeltaF508/DeltaF508 (n=12)	-	-	-	-
DeltaF508/N1303K (n=1)	-	-	-	-
DeltaF508/ Unknown/Nepoznat (n=11)	-	-	-	-
Unknown/Nepoznat (n=1)	-	-	-	-
[2]FEV1 (%) (n=16)	67.3	24.1	21	101
< 40% (n=3)	-	-	-	-
40-69% (n=5)	-	-	-	-
> 70% (n=85)	-	-	-	-

[1]Body mass index/Indeks tjelesne mase; [2]Forced expiratory volume/Forsirani ekspiratorni volumen.

of 25 patients showed pathological gastroesophageal reflux (Table 2).

Mean fasting gastric pH was 1.35 and the increase of pH after food consumption was moderate (2.8) (Table 3). We observed a significant positive correlation between the age and reflux index ($r = 0.793$, $p = 0.006$) and also between FEV1 and the fasting gastric acidity ($r = 0.776$, $p = 0.04$). A significant negative correlation was found between FEV1 and reflux index ($r = -0.802$, $p=0.03$) and between age and fasting gastric acidity ($r= -0,775$, $p = 0.008$). There was a negative, but not significant correlation between FEV1 and age ($r = -0.726$, $p = 0.06$).

Diurnal pH monitoring (Table 4) yielded significantly more episodes of reflux than the nocturnal. During the nocturnal period the episodes of refluxes were significantly longer. Mean gastric and oesophageal pH were significantly lower during night. Although reflux indexes were higher during the day, these differences were not significant.

Table 2 *Pathological gastroesophageal reflux in Cystic fibrosis patients (N=25)*
Tabela 2 *Patološki gastroezofagealnui refluks u bolesnika s cističnom fibrozom (N=25)*

Age of patients/Dob bolesnika	Reflux indeks/Refluksni indeks		
	5 - 10	10.1 - 20	>20
Preschool/Predškolska djeca (n = 3/10)	2	1	
School/Školska djeca (n = 10/15)	5	1	4
Total/Ukupno (n = 13/25)	7	2	4

Table 3 *Results of 24-hour simultaneous oesophageal and gastric pH monitoring*
Tabela 3 *Rezultati 24 satnog simultanog ezofagealnig i gastričnog monitoriranja*

Number of patient/Broj pacijenta	Age (years)/ Dob (godine)	FEV[1] (%)	Reflux index (%)/ Refluksni indeks (%)	pH gastric/pH želuca	
				Fasting/ Natašte[2]	After meal/ Poslije jela[3]
1	0.25	-	4.3	1.6	6.4
2	3	-	2.6	2.2	3.0
3	3	-	2.2	1.7	2.2
4	7	38	10.1	0.9	3.0
5	8	56	3.6	1.4	2.8
6	8	52	6.5	1.5	2.2
7	8	62	4.4	1.4	2.9
8	14	47	17.1	0.9	1.6
9	15	39	7.1	1.0	2.4
10	18	21	23.8	0.9	1.5
$\bar{\chi} \pm$ SD	8.4±5.7	45±13.8	8.1±7.1	1.35±0.4	2.8±1.4

[1]Forced expiratory volume in 1st second/Forsirani ekspiratorni volumen u prvoj sekundi; [2]One hour prior to next feeding/Jedan sat prije narednog jela; [3]Immediately after feeding/Odmah nakon hranjenja.

Table 4 *Results of diurnal versus nocturnal esophageal pH monitoring (N=25)*
Table 4 *Dnevni i noćni ezofagealni monitoring (N=25)*

Parameters/Parametri ($\bar{\chi}\pm$ SD)	Day	Night	t	p
Oesophageal pH/Esofagealni pH	5.84 ± 0.61	5.57 ± 0.75	2.17	0.040
Number of refluxes/Broj refluksa	102.3 (91.4)	42.9 (45.8)	3.82	0.001
Number of refluxes longer than 5 minutes/ Broj refluksa dužih od 5 minuta	2.0 (4.7)	2.2 (2.83)	-0.24	0.814
Longest reflux in minutes/Najduži refluksa u minutama	9.5 (18.1)	32.8 (48.4)	-2.60	0.016
Reflux index/Refluksni indeks	10.4 (10,95)	8.4 (11.8)	0.70	0.438
Oscillatory index/Oscilatorni indeks	4.0 (4.06)	5.0 (6.3)	-0.94	0.356
Gastric pH/Želučani pH	2.1 (0.75)	1.6 (0.70)	6.4	0.001

Discussion

In recent years knowledge about the basic defects in CF has increased enormously. Nevertheless, there are numerous unsolved problems in the diagnosis and treatment of CF patients (23). Gastroesophageal reflux is frequently recognised in cystic fibrosis patients, with a reported incidence between 25% and 100%. The relationship between GER and lung complications in CF is not well understood (3-12). Pathological GER was found in about one half of our CF patients and it was present mainly in school-aged children. In 1988 Dab and Malfroot described pathological gastroesophageal reflux in all ten reported infants and newborns with cystic fibrosis. Their first hypothesis was that GER is inevitably present in every baby with CF (10). In 1991, the same authors observed pathological GER in 81% CF patients younger than 60 months and found a significant negative correlation between age and the severity of GER (9). Heine et al (5) found that about one fifth of newly diagnosed infants with cystic fibrosis have pathological gastroesophageal reflux.

Gustafson et al. observed pathological gastroesophageal reflux in 9 out of 12 cystic fibrosis patients (median age 14.4 years), mainly in subjects with deteriorated lung function (4). Our study confirmed this observation as we have shown a highly significant negative correlation between FEV1 and the reflux index, but not between age and FEV1. Some investigators suggested that gastroesophageal reflux may occur secondary to lung disease. They proposed that hyperinflation and stetting of the diaphragm caused widening of the angle of His and impairment of gastroesophageal competence (24, 25).

Cucchiara et al showed that the predominant reflux mechanism in cystic fibrosis patients is a transient inappropriate lower oesophageal sphincter relaxation rather than low steady state, basal lower oesophageal sphincter pressure (3). Studies of gastric emptying in cystic fibrosis have provided conflicting results. Several reports have reported that gastric emptying is normal or faster (26, 27). Using different methodologies others have shown that gastric emptying in CF patients is delayed (28, 29). Except in preterm infants, delayed gastric emptying and GER are linked by a physio-pathological relationship and the degree of GER is related to the rate of gastric emptying (29).

Gastric acid hyper secretion, common in patients with CF, may be an important additional factor in gastroesophageal reflux disease. Johansson et al found in subjects with pathological GER but without pulmonary symptoms that gastric hypersecretion was common (66%) (30). Although most studies noted that CF patients have gastric acid hyper secretion (13, 14), there are some studies which did not find a significant difference between healthy subjects and CF patients (15, 16). In 1996, Gregory showed that in both groups, in CF patients and healthy subjects, the fasting values generally varied between pH 1 and 3 and that there was an increase of gastric pH up to 5 after meal. In the present study mean fasting gastric pH was quite low (1.35), and after meal a moderate increase of pH was seen in all patients except in those with extremely deteriorated pulmonary function (FVC 27%, FEV1 21%). We observed a positive correlation between FEV1 and fasting gastric acidity and also between the age and reflux index. A highly significant negative correlation was found between fasting gastric acidity and age, as well as between fasting gastric acidity and reflux index. Antimony electrodes, which we used in our study, are not ideal for low pH ranges and the error of measuring is too large to make a conclusion from our findings possible. We did measure gastric pH, but true acidity should be determined by a titration of timed samples of gastric juice, which would have required standardized meals.

In this study we found significant differences between variables of pH monitoring during day and night. Day-night differences are not different from other children with GER but without CF (31, 32). Through the night we observed more episodes of long refluxes and lower mean oesophageal pH. Gastric hyperacidity became more marked through the night. Only the number of reflux episodes was higher during the diurnal period. Several studies have claimed that gastroesophageal reflux is more frequent during alert periods then during sleep periods, but nocturnal reflux might be a contributory factor in identification of children with respiratory symptoms related to gastroesophageal reflux (17, 20, 33).

Conclusion

In conclusion, our results suggest that the method of choice for the diagnosis of gastroesophageal reflux in cystic fibrosis patients should be simultaneous monitoring of oesophageal and gastric pH including alert and sleep periods. Gastric acid hyper secretion and reduced lung function facilitate gastroesophageal reflux, which in turn might contribute to the progression of the pulmonary disease as seen in our cystic fibrosis patients. The role of gastroesophageal reflux as a contributor to the development of lung disease should be properly investigated in children with cystic fibrosis and needs further study.

Conflict of Interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organisation.
Sukob interesa: autori su se izjasnili da nisu u sukobu interesa. Studija nije bila sponzorirana od neke vanjske institucije.

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Sažetak

GASTROEZOFAGEALNI REFLUKS I ŽELUČANI HIPERACIDITET U PACIJENATA SA CISTIČNOM FIBROZOM

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Uvod Gastroezofagealni refluks (GER) je čest u djece s cističnom fibrozom (CF). Uloga želučanog hiperaciditeta u nastanku GER-a još uvijek nije dovoljno razjašnjena.
Ispitanici i metode U 25 djece s CF učinjen je 24 satni ezofagealni pH monitoring. Od svakog pH monitoringa odabran je dnevni i noćni period a u 10 bolesnika istovremeno je proveden 24-pH monitoring jednjaka i želuca.
Rezultati U 13 od 25 djece s CF dokazan je patološki GER. Tijekom dana češće su refluksne epizode u odnosu na noćni period. Noćni pH monitoring pokazao je znatno veći broj refluksnih epizoda u trajanju duže od 5 minuta, kao i niži srednji želučani i ezofagealni pH.
Zaključak Metoda izbora za dijagnozu gastroezofagealnog refluksa u djece s CF je simultani ezoofagealni i želučani 24-satni pH monitoring, uključujući razdoblja dana i noći. Pojačana želučana kiselost i smanjene plućne funkcije olakšavaju refluks, što posljedično može doprinijeti progresiji plućnog oboljenja kao što je i uočeno u naših bolesnika s CF.

Ključne riječi: Cistična fibroza ▪ Gastroezofagealni reflux ▪ Želučani hiperaciditet ▪ Djeca ▪ Plućna funkcija ▪ pH monitoring

Primljeno: 29. 7. 2009.
Prihvaćeno: 18. 11. 2009.