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Gastroesophageal reflux in children with functional constipation

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Background/aims: *Functional constipation and gastroesophageal reflux disease are two major and commonly encountered components of childhood functional gastrointestinal disorders. Epidemiological studies in the adult population support that there is a significant overlap between the different functional disorders of the digestive tract. Therefore, we aimed to investigate the frequency of gastroesophageal reflux disease in children with functional constipation and to compare clinical findings and 24-h esophageal pH monitoring with a group of patients with suspected gastroesophageal reflux disease.* ***Materials and Methods:*** *Children between 4 and 16 years old with functional constipation (based on Rome III criteria, Group 1; n=38) were prospectively evaluated. A control group was composed of patients with symptoms suggesting gastroesophageal reflux disease (Group 2; n= 40). All patients included in the study were asked about reflux-related symptoms, and then all cases underwent 24-h esophageal pH monitoring analysis.* ***Results:*** *Delayed gastric emptying symptoms such as belching and hiccups were more common in patients in Group 1 (p=0.002, p=0.021, respectively), whereas chronic cough was more common in patients in Group 2 (p=0.012). According to the 24-h esophageal pH monitoring, pathologic acid reflux in the lower and/or laryngopharyngeal portion of the esophagus was determined in 39.5% of the patients in Group 1 and in 42.5% of the patients in Group 2 (p=0.96). No significant difference was found in terms of age, gender and duration of constipation in patients with and without acid reflux in Group 1 patients. Pyrosis (66.6 vs. 0%, p=0.00001) was more common in Group 1 patients with acid reflux, but hiccups (20 vs. 69.5%, p=0.007) and belching (33.3 vs. 60.8%, p=0.184) were more common in patients in Group 1 without acid reflux.* ***Conclusions:*** *Gastroesophageal reflux disease should be considered in the treatment and monitoring of patients with functional constipation. Further studies are needed using 24-h pH multi-channel impedance.*

Key words: Children, functional constipation, gastroesophageal reflux disease

Fonksiyonel konstipasyonlu çocuklarda gastroözofageal reflü

Giriş ve Amaç: *Amacımız, fonksiyonel konstipasyonlu çocuklarda gastroözofageal reflü hastalığı sıklığını saptamak, klinik bulgular ve 24 saatlik pH monitorizasyon bulgularını, klinik olarak gastroözofageal reflü hastalığı düşünülen olgularla karşılaştırmaktır.* ***Gereç ve Yöntem:*** *Dört-16 yaş arasında Roma III kriterlerine göre fonksiyonel konstipasyon tanısı alan (Grup 1) 38 çocuk hasta değerlendirilmiştir. Kontrol grubu olarak klinik olarak gastroözofageal reflü hastalığı düşünülen 40 olgu (Grup 2) alınmıştır. Tüm hastalarda reflü semptomu ile ilişkili semptomlar değerlendirilmiş ve olgulara 24 saatlik pH monitorizasyonu uygulanmıştır. Her iki grubun bulguları değerlendirilmiştir.* ***Bulgular:*** *Hıçkırık ve geğirme gibi gecikmiş mide boşalım bulguları Grup 1'de en sık görülen semptomlardı (sırasıyla, p=0.002, p=0,02). Buna karşın kronik öksürük Grup 2'de en sık göülen semptomdu (p=0.01). Yirmidört saatlik pH monitorizasyon bulgularına bakıldığında özofagusun üst ve/veya alt probunda patolojik asit reflü oranı sırasıyla Grup 1'de %39.5 iken Grup 2'de %42.5 olarak saptandı (p=0.95). Grup 1 olgularda patolojik asit reflü olan ve olmayan hastalar karşılaştırıldığında; yaş, cinsiyet, konstipasyon süreleri arasında farklılık saptanmadı, pirozis patolojik asit reflüsü olanlarda en sık bulgu iken (p=0.0001), hıçkırık ve geğirme patolojik asit reflüsü olmayan hastalarda sık bulguydu (sırasıyla p=0.007, p=0.1).* ***Sonuç:*** *Gastroözofageal reflü hastalığı fonksiyonel konstipasyonlu çocukların takip ve izleminde düşünülmelidir. Bu konuda özellikle 24 saatlik pH-multi kanal impedans yöntemi ile daha ileri çalışmalara ihtiyaç vardır.*

Anahtar kelimeler: Çocuklar, fonksiyonel konstipasyon, gastroözofageal reflü hastalığı

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INTRODUCTION

The enteric nervous system (ENS) modulates motility, secretions, microcirculation, and immune and inflammatory responses of the gastrointestinal (GI) tract (1). The adaptive response capability of ENS to physiological and stressful triggers has been suggested to lead to the development of functional gastrointestinal disorders (FGID). Functional GI system diseases represent one of the disorder groups in which the incidence is gradually increasing due to changing living conditions and nutritional habits among children. In most children, constipation is functional, that is, without objective evidence of a pathological condition. It constitutes 1.2% of referrals to pediatric clinics and 8.3% of those to pediatric gastroenterology clinics (2).

Functional constipation (FC) and gastroesophageal reflux disease (GERD) are two major and commonly encountered components of childhood FGID. Little is known about the pathogenesis of these diseases, though they are believed to be caused by hormonal, neuronal and psychogenic elements. Insufficient data exist as to whether or not FGIDs emerge in combination during childhood. Colonic transit time in FC generally lengthens, and intraabdominal pressure thus increases temporarily during defecation (3,4). Many children suffering from constipation experience upper GI symptoms, including early satiety, frequent heartburn, and intermittent vomiting, all of which improve or resolve once the constipation has been adequately treated. Additionally, Borrowitz and Sutphen (5) described constipation in children suffering from persistent GERD.

Since various functional intestinal diseases may overlap, the interrelation between reflux and constipation is a matter of wide interest. This study was intended to investigate the frequency of GERD in children with FC and to compare clinical findings and other parameters with a group of patients with suspected reflux disease.

MATERIALS AND METHODS

Children between 4 and 16 years old and referred to our pediatric gastroenterology outpatient clinic with a complaint of constipation were prospectively evaluated. Diagnosis of FC was based on the Rome III criteria (6). Patients were excluded if they had mental/motor retardation, abnormal thyroid function tests, documented food allergy or any organic cause. Fifty-one patients with constipation were admitted during the study period, but 13 cases were excluded for both exclusion criteria and rejection of the study design (Group 1, n: 38).

No control group consisting of healthy children could be established as ethical committee approval could not be obtained. A control group was formed of patients who admitted to our pediatric gastroenterology outpatient clinic with symptoms suggesting GERD (Group 2, n: 40). FC was ruled out in this group on the basis of symptoms and Rome III criteria.

Demographic and clinical findings were recorded in patients with FC. Then, all patients (Groups 1 and 2) included in the study were asked about reflux-related symptoms and symptoms suggestive of delayed gastric emptying, such as hiccups and belching. After a symptom questionnaire, all cases underwent 24-hour (h) esophageal pH monitoring analysis. Antimony dual canal (sensor spacing 5 or 10 cm) probes were used according to patients' ages for recording purposes. Subjects over five years old were provided with 24-h esophageal pH monitoring recording apparatus (Orion II, MMS, the Netherlands) using 10 cm signal internal pH meter probes, while those aged under five were given 5 cm signal probes. 24-h esophageal pH monitoring was commenced following 8-h nocturnal fasting. Medical treatments were stopped seven days before the procedure in patients with suspected GERD. The pH meter electrodes were calibrated using pH 7 and pH 1 buffer solution prior to placement. The distal end of the pH meter probe was inserted into the esophagus nasopharyngeally at a point corresponding to 87% of the esophageal length as confirmed by X-ray graphics. The proximal probe was localized to the upper esophageal sphincter. Children were sent home after pH meter measurement commenced, and they and their families were given comprehensive information regarding appropriate feeding. Results recorded were analyzed and interpreted using Database software (version 8.3g, MM, the Netherlands). An acid reflux episode is defined as esophageal pH <4 for at least 15 seconds (s). 2001 NASPGHAN distal probe pH limits were taken for diagnosis of GERD: total number of acid reflux episodes (pH <4/24 h) >50; number of episodes of acid reflux (pH <4/24 h) lasting more than 5 min >6; the percentage of time with pH <4 (%), and a total acid reflux index (RI) >5.4% in the distal probe were used as criteria (7,8). Using the proximal probe, patients

with a total RI >1.2% and pH <4 were considered to have pharyngolaryngeal reflux (PLR) (9,10). Patients meeting any of these criteria were regarded as having pathological acid reflux.

Ethical Committee approval was granted for the study.

Statistical Analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences. Results were expressed as mean (±standard deviation) and percentage. Student's t-test was used to compare the two groups. Chi-square test was used where appropriate. $p<0.05$ denoted a statistically significant difference.

RESULTS

The mean age of the study population was 8 ± 3.9 (M/F, 17/21) and 8±3.2 (M/F, 20/20) years in Groups 1 and 2, respectively ($p>0.05$). Mean duration of constipation in Group 1 was 24.7±25.9 months (range: 3-120 months).

Reflux-Related Symptoms

The most frequent symptoms in Group 1 were belching and hiccups (n=19, 50%), followed by coughing and regurgitation (n=18, 47.4%). In Group 2, the most frequent symptoms were chronic cough (n=30, 75%) and regurgitation (n=28, 70%) (Table 1). Delayed gastric emptying symptoms such as belching and hiccups were more common in patients with FC (p=0.002, p=0.021, respectively), whereas chronic cough was more common in patients with reflux-related symptoms (p=0.012).

24-h Esophageal pH Monitoring

According to the 24-h esophageal pH monitoring, pathologic acid reflux in the lower and/or laryngopharyngeal portion of the esophagus was determined in 39.5% (15/38) of the patients in Group 1 and in 42.5% (17/40) of the patients in Group 2 (p=0.96). Pathologic acid reflux in the distal channel was determined in 26.3% of the patients, whereas pathologic acid reflux (RI% >1.2) in the proximal channel was seen in 34.2% (n=13) of the patients in Group 1. Acid reflux in the distal and proximal channel was seen in 32.5% and 30% of the patients in Group 2, respectively (p=0.86, p=0.75, respectively). A comparison of the 24-h esophageal pH monitoring results in patients with FC (Group 1) and in patients with suspected GERD (Group 2) is shown in Table 2.

Table 1. Reflux-related symptoms and respiratory diseases in Group 1 and Group 2

Parameters	Group 1 (n=38)	Group 2 (n=40)	P value
Vomiting, n (%)	7 (18.4)	11 (27.5)	0.456
Regurgitation, n (%)	18 (47.4)	28 (70)	0.071
Hoarseness, n (%)	12 (31.6)	12 (30)	0.924
Pyrosis, n (%)	10 (26.3)	17 (42.5)	0.206
Hiccups, n (%)	19 (50)	9 (22.5)	**0.021**
Belching, n (%)	19 (50)	6 (15)	**0.002**
Chronic cough, n (%)	17 (47.4)	30 (75)	**0.012**
Wheezing, n (%)	10 (26.3)	16 (40)	0.297
Pneumonia/bronchitis, n (%)	9 (23.7)	12 (30)	0.708

Group 1: Patients with functional constipation. Group 2: Patients with suspected gastroesophageal reflux disease.

Table 2. 24-h esophageal pH monitoring according to groups

24-h esophageal pH recording parameter	Group 1 (n=38)	Group 2 (n=40)	P value
Distal probe RI >5.4%, n (%)	10 (26.3)	12 (30)	0.95
Proximal probe RI >1.2%, n (%)	13 (34.2)	13 (32.5)	0.86
Proximal and/or distal probe positivity, n (%)	15 (39.5)	17 (42.5)	0.75
Patients with total number of acid reflux episodes >50, n (%)	3 (7.8)	3 (7)	0.67
Patients with total number of episodes of acid reflux lasting more than 5 min >6, n (%)	8 (21)	14 (35)	0.26
RI distal (%), mean (min-max)	3.36 (0.3-14)	3.53 (0.2-14)	0.82
RI proximal (%), mean (min-max)	1.08 (0-4.4)	.97 (0-3.9)	0.61

RI: Reflux index (reflux time pH <4%). Distal: Distal esophageal probe. Proximal: Proximal esophageal probe.

No significant difference was found in terms of age, gender and duration of constipation in patients with and without acid reflux in Group 1. Pyrosis (66.6 vs. 0%, p=0.00001) and (66.6 vs. 0%, p=0.00001) were more common in patients with acid reflux, but hiccups (20 vs. 69.5%, p=0.007) and belching (33.3 vs. 60.8%, p=0.184) were more common in patients without acid reflux.

A second comparison was performed between 15 subjects in Group 1 and 17 in Group 2 with pathological acid reflux as shown by 24-h esophageal pH monitoring (Table 3). Regurgitation and chronic cough were more common in patients with reflux-related symptoms (Table 3).

A total of 34.2% (n=13) of cases in Group 1 exhibited PLR findings on 24-h pH meter measurement compared to 31.5% (n=12) in Group 2 (p>0.05). Clinical findings of the 13 cases diagnosed with PLR are presented in Table 4.

DISCUSSION

Functional gastrointestinal system diseases (FGIDs) are a group of childhood disorders, our knowledge of which is relatively limited. More importantly, the different subgroups among such disease groups are closely interrelated, and their natural courses and interrelations have yet to be fully clarified. FC and GERD are most frequently seen among these groups. However, evidence as to whether any relationship exists between them is limited.

Epidemiological studies in the adult population support the idea that there is a significant overlap between the different functional disorders of the digestive tract (11). We found acid reflux in 39.5% of constipated children, a level similar to that in children presenting with reflux symptoms. Visceral oversensitivity and GI dysmotility are the main pathophysiological mechanisms involved in FGID (11). Increased incidence of acid reflux in patients with FC may suggest that two distinct disorders may have similar pathophysiology, or presence of chronic constipation may predispose to acid reflux. Altered colonic transit motility is the main contributing factor in the pathophysiology of chronic constipation. In general, it is speculated that there is a general smooth-muscle dysfunction of the GI tract in chronic constipation that may explain the relation with GERD. The association of irritable bowel syndrome (IBS) with GERD was well defined in previous adult studies, ranging from 30-50%. Constipation associated with GERD was studied in only one adult study, and it was found that GERD-related symptoms were observed

Table 3. Comparison of the symptoms and respiratory diseases between the patients with acid reflux in Group 1 and Group 2

Symptoms	Group 1 (n=15)	Group 2 (n=17)	P value
Vomiting, n (%)	2 (13.3)	3 (17.6)	0.56
Regurgitation, n (%)	10 (66.7)	16 (94.1)	**0.05**
Hoarseness, n (%)	7 (46.7)	5 (29.4)	0.52
Pyrosis, n (%)	10 (26.3)	7 (41.1)	0.27
Hiccups, n (%)	3 (20)	2 (11.7)	0.43
Belching, n (%)	5 (33.3)	3 (17.6)	0.26
Chronic cough, n (%)	8 (53.3)	15 (88.2)	**0.028**
Wheezing, n (%)	6 (40)	7 (41.1)	0.76
Pneumonia/bronchitis, n (%)	2 (15)	3 (17.6)	0.73

Table 4. Symptoms compared between PLR-positive and PLR-negative patients with functional constipation

Symptoms	PLR-positive (n=12)	PLR-negative (n=26)	P value
Wheezing (%, n)	16% (2)	23% (6)	0.5
Coughing (%, n)	66% (8)	38% (10)	0.1
Bronchitis (%, n)	16.6% (2)	15% (4)	0.5
Regurgitation (%, n)	25% (3)	35% (9)	0.1
Hoarseness (%, n)	41.6% (5)	23% (6)	0.1

PLR: Pharyngolaryngeal reflux.

in 32.9% of the IBS-constipation-predominant patients diagnosed by Rome II criteria (11).

The association of constipation with reflux-related symptoms was first defined by Borrowitz et al. (5). They reported 34 children with evidence of GERD who were resistant to classical therapy. Many of them underwent extensive laboratory, radiological and endoscopic examinations. All children were found to have constipation and all children experienced resolution of their chronic upper GI symptoms after adequate management of their constipation. They suggested that unrecognized constipation may cause upper GI symptoms, and that extensive laboratory evaluations must be delayed until chronic constipation is ruled out and treated. Duodenogastric reflux, alkaline reflux and increased intraabdominal and intragastric pressures may play a role in GERD in cases with FC (5,11). Prolonged transit time may contribute to delay in gastric emptying, and patients may present with severe reflux- related symptoms (12).

Despite the higher prevalence of delayed gastric emptying symptoms, such as hiccups and belching, in patients with FC compared to patients with reflux-related symptoms, they were seen less frequently in patients with acid reflux with FC. More frequent observation of hiccups and belching in cases with constipation suggests a possible gastric emptying failure and elevation of intraabdominal and intragastric pressures. However, subgroup analysis in our study revealed that different mechanisms may be responsible for the acid reflux. Similar to our study, Salvatore et al. (13) studied a group of infants with GERD and found that children with constipation had a 48% RI positivity according to the pH meter, higher than without constipation. Further, they failed to establish any significant relationship between belching, hiccups, coughing, or regurgitation and abnormal pH meter findings.

The limitations of our study are: (i) We were unable to determine the non-acid reflux level in the study group. The study should, therefore, have been conducted using a 24-h pH multi-channel impedance technique, and (ii) We were not able to compare our results with a healthy control group.

In conclusion, GERD should be considered in the treatment and monitoring of patients with FC. Further studies are needed using 24-h pH multichannel impedance.

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