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Kronik idiopatik yavaş transitli konstipasyonlu hastalarda safra kesesi motilitesi

Gallbladder motility in patients with chronic idiopathic slow transit constipation

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Bacground/aims: *It has been reported that other gastrointestinal organs than the colon may be involved in slow transit constipation. In this study, gallbladder motility in slow transit constipation was investigated.* ***Methods:*** *Thirty seven patients (30 female, seven male, mean age 48 years) with chronic idiopathic constipation (£2 defecations/week for >2 years) were included in the study and colon transit scintigraphy was performed. Slow transit constipation was defined as total colonic transit time >72 hours. Gallbladder motility was scintigraphically analyzed with standard liquid diet (normal gallbladder ejection fraction >40%).* ***Results:*** *Slow transit constipation was observed in 24 of 37 (64.8%) patients. Colonic transit time was <72 hours in 13 (35.1%) patients, 73-96 hours in six (16.2%) patients, 97-120 hours in 16 (43.2%) patients and >144 hours in two (5.4%) patients. There were no patients with a transit time of 121-144 hours. Segmental slowing was observed at the right colon in one (4.1%), left colon in three (12.5%), pancolonic region in three (12.5%), rectosigmoid in four (16.7%) and left colon with rectosigmoid in 13 (54.2%) of the 24 patients. Gallbladder dysmotility was observed in eight of 18 (44.4%) patients with slow transit constipation. Mean gallbladder ejection fraction was 41.6±13.6% (16.3-67.0%). Delaying of colonic transit time and slowing of segmental gut transit were not quantitatively related with decreased gallbladder ejection fraction.* ***Conclusion:*** *Slow transit constipation may be associated with impaired function of other gastrointestinal organs. Approximately half of patients with slow transit constipation also have gallbladder dysmotility. Slow transit constipation may not be a purely colonic pathology, but may be a component of a generalized gastrointestinal motility disorder involving several organs.*

Key words: Chronic idiopathic slow transit constipation, colon transit scintigraphy, gallbladder motility.

Amaç: *Yavaş transitli konstipasyonda diğer gastrointestinal organlarda da fonksiyon bozuklukları olabildiği sınırlı sayıdaki çalışmalarla bildirilmiştir. Bu çalışmada yavaş transitli konstipasyonlularda safra kesesi motilitesini araştırdık.* ***Yöntem:*** *37 kronik idiopatik konstipasyonlu hasta (30K, 7E, ortalama yaşları 48 yıl, dışkılama sıklığı ≤2/hafta ve >2 yıl) çalışmaya alındı. Hastalara radyonüklid kolon transit sintigrafisi uygulandı. Kolon transit süresi >72 saat olanlar yavaş transitli konstipasyonlu olarak kabul edildiler. Yavaş transitli konstipasyonlularda standart sıvı gıda ile kolesintigrafik olarak safra kesesi motilitesi (normal safra kesesi ejeksiyon fraksiyonu >%40) araştırıldı.* ***Bulgular:*** *Yavaş transitli konstipasyon 37 hastadan 24'ünde (%64.8) saptandı. Kolon transit süresi 13 hastada (%35.1) <72 saat, 6'sında (%16.2) 73-96, 16'sında (%43.2) 97-120, 2'sinde (%5.4) >144 saat idi. 121-144 saat arasında hiç hasta yoktu (%0). Yavaş transitli konstipasyonlu 24 hastanın segmental kolon transit yavaşlaması incelendiğinde sağ kolon tutulumu 1 (%4.1), sol kolon 3 (%12.5), pankolonik 3 (%12.5), rektosigmoid 4 (%16.7) ve sol kolon ile rektosigmoid 13 hastada (%54.2) gözlendi. 18 yavaş transitli konstipasyonludan 8'inde (%44.4) safra kesesi dismotilitesi saptandı. Ortalama safra kesesi ejeksiyon fraksiyonları %41.6±13.6 (%16.3-67.0) idi. Kolon transit süresinin uzaması ve kolonda segmental yavaşlama ile safra kesesi ejeksiyon fraksiyonu düşüklüğü arasında kantitatif ilişki ve korelasyon saptanmadı.* ***Sonuç:*** *Yavaş transitli konstipasyon diğer gastrointestinal organların fonksiyon bozuklukları ile birlikte olabilir. Yavaş transitli konstipasyonluların yaklaşık yarısında safra kesesi dismotilitesi saptanmaktadır. Kronik idiopatik yavaş transitli konstipasyon çoğu zaman sadece kolonun bir patolojisi olmayıp gastrointestinal sistemin birden fazla organını tutabilen yaygın bir motilite bozukluğunun komponenti olabilmektedir.*

Anahtar kelimeler: Kronik idiopatik yavaş transitli konstipasyon, kolon transit sintigrafisi, safra kesesi motilitesi.

INTRODUCTION

Severe chronic constipation can be subdivided into outlet obstruction, slow transit constipation (STC) and normal transit constipation (1). Chronic idiopathic constipation caused by STC is one of the most common forms of constipation, which is characterized by a lifelong history with no identifiable etiologic factor. Bowel action may be once every two to three weeks. On investigation, these patients have a normal barium enema, delay in passage of inert markers through the gastrointestinal tract and frequently normal rectal emptying.

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The cause of STC is still uncertain, and many theories have been proposed, including insufficient intake of dietary fiber, a hormone disorder (2) and various degrees of intestinal neuronal agenesis (3). However, the frequent observation that patients with STC have other disturbances involving the stomach (4), small bowel (5), anorectal function, the bladder (6), blood pressure control (7) and gastrointestinal hormone release (8) suggest that it could be a pangastrointestinal motility disorder.

In this study, gallbladdeı (GB) function was analyzed by scintigraphy in a series of patients with severe, chronic STC with the aim of detecting any abnormality as a component of pangastrointestinal motility abnormality.

MATERIALS AND METHODS

The study included 37 patients with chronic idiopathic constipation referred to Gülhane Military Medical Academy, Haydarpaşa Training Hospital, Department of Gastroenterology between March 1999 and April 2000.

All patients reported two or more of the criteria for constipation as defined by an international panel in Rome in 1995 (9):

1. Two or fewer bowel movements per week at least 25% of the time

2. sensation of incomplete evacuation at least 25% of the time

3. lumpy and/or hard stools at least 25% of the time

4. straining at defecation at least 25% of the time.

Patients with constipation who had undergone more than two years of unsuccessful treatment with dietary fiber supplements and oral laxatives entered the study.

The exclusion criteria were as follows:

1. organic colonic disease shown by colonoscopy and/or barium enema

2. previous abdominal surgery

3. diabetes or other systemic metabolic disease

4. gallstones confirmed by ultrasound (USG).

Colon transit scintigraphy (CTS) was performed on all patients with severe, chronic, idiopathic constipation. Also, GB functions of patients with STC were evaluated by scintigraphy.

Colon Transit Scintigraphy

All patients underwent CTS. During the test week, oral laxatives or cleansing enemas were withdrawn. No effort was made to control the patients' diet during the scanning period.

Subjects attended the nuclear medicine department on a Monday morning and were given 10-11 MBq [^{67}Ga]citrate orally at approximately 09^{00} hrs. They returned the same day at approximately 14^{00} hrs and on subsequent days at approximately 24, 48, 72, 96, 120, and 144 hrs following the oral administration. On each occasion, anterior and posterior abdominal views were obtained for 10 min using a large field-of-view gamma camera (ADAC Genesys) and medium energy collimator (peaked for 93 KeV, 185 KeV, 300 KeV). To allow for tissue attenuation, each view was immediately followed by a posterior view. Radioisotope counts were quantitatively determined. Regional colonic radioisotope movement was assessed from regions of interest (ROI) created by visually analyzing the full sequence of scans (caecum and ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and rectum). Time activity curves for each ROI allowed evaluation of the proportion of radioisotope spent in each region over the scanning period, thus clarifying the site of segmental colonic delay. Slow total colonic transit was defined as > 72 hr (10).

Gallbladder Motility

After an overnight fast, subjects attended the nuclear medicine department at 11^{00} hrs. All patients with STC were given 5 mCi ^{99m}Tc-labeled trimethyl-3-bromo iminodiacetic acid (HIDA) as an intravenous bolus. With patients in the supine position, anterior images of the GB were acquired in 60-sec time frames in a 64x64 matrix using a gamma camera (ADAC Genesys) with a low-energy parallel collimator (peaked for 140 KeV±20% window) linked to a Pegasys-Sun computer system. Regions of interest were drawn around the GB and time activity curves were generated after correction for background.

Once GB activity peaked, each patient drank a liquid test meal (30% lipid, 16.7% protein, 53% carbohydrate [Ensure Plus-Abbott, 375Kcal/ 250 ml]) at room temperature over a one minute period. Following completion of the test meal, data acquisition was continued for a further 30 min. Time of onset and completion of GB contraction

Table 1. Characteristics of patients with slow and normal transit constipation

	Total (n: 37)	*STC (n: 24)*	*NTC (n: 13)*	*P(*)*
Age (years±SD)	48.3±17.8	49.2±18.6	46.3±16.8	0.66
Female/Male	30/7	18/6	12/1	0.20
Duration of constipation (years) (**)	8 (2-50)	7.5 (2-50)	10 (2-35)	0.55
Defecation frequency (once in days±SD)	6.6±2.6 (4-14)	6.3±2.8 (4-14)	5.8±1.9 (4-10)	0.12

*Comparison of patients with slow and normal transit constipation
**Median (min-max)
STC: Slow transit constipation, NTC: Normal transit constipation

were identified by time activity curves for each individual. Gallbladder ejection fraction (GBEF) was calculated as net peak fasting activity – net through postprandial activity/net peak fasting activity X 100.

The lower limit of normal GBEF was accepted as 40% (11). GBEF<40% was defined as biliary dyskinesia.

Statistical Analysis

Data were analyzed using the statistical software packages SPSS 7.5 for Windows. Results were expressed as mean (and SD or SEM) or median (min-max). One group Kolmogorov-Smirnov test was used for normal distribution. Statistical comparisons for were made using t-test, chi-square test and Fisher's exact chi-square test. Correlation results were calculated with Pearson test. The level of significance was set at $p<0.05$.

RESULTS

The 37 patients with chronic idiopathic constipation included 30 females and seven males with a mean age of 48.3±17.8 years (range, 19-86 years). The mean duration of constipation was eight years (range: 2-50 years). The number of spontaneous defecations ranged between one every four to one every 14 days, with a mean of every seven days.

All 37 patients underwent evaluation of colonic

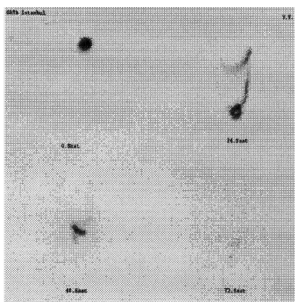

Figure 1a. Colon transit scintigraphy of a patient with normal transit constipation. All radioisotope had left the colon at 72 hr.

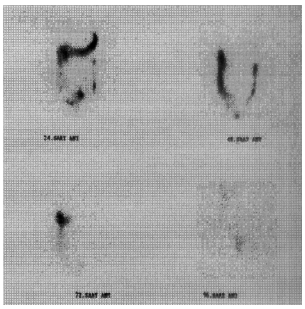

Figure 1b.Segmental slowing in the right colon. The bulk of the isotope is seen to reside in the right colon after 72 hr.

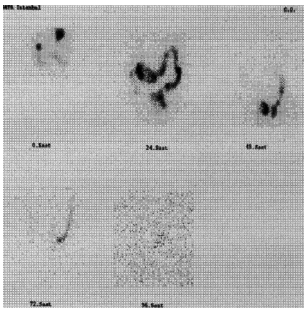

Figure 1c. Segmental slowing in the left colon. The bulk of the isotope is seen to reside in the left colon after 72 hr.

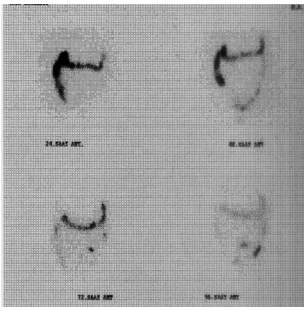

Figure 1d. Pancolonic inertia. The bulk of the isotope is seen to reside in the all regions of the colon at 72-96 hr.

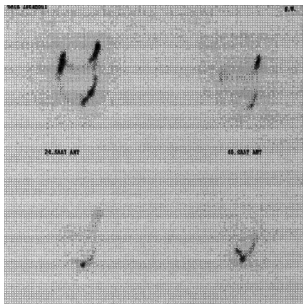

Figure 1e. Segmental slowing in the rectosigmoid region. The bulk of the isotope is seen to reside in the rectosigmoid region at 72-96 hr.

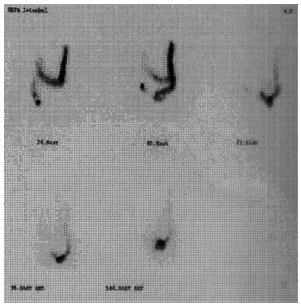

Figure 1f. Segmental slowing in the left colon and rectosigmoid region. The bulk of the isotope is seen to reside in the left colon and rectosigmoid region at 72-144 hr.

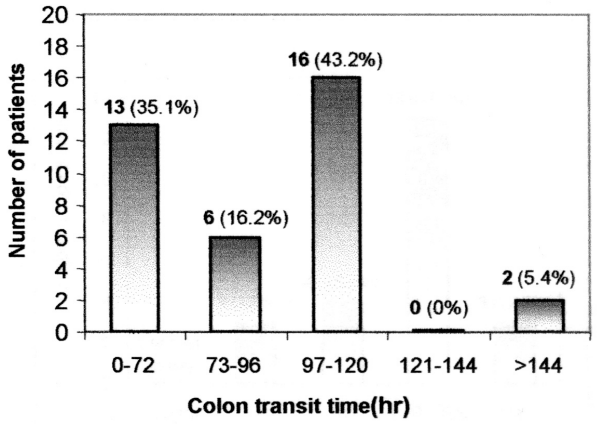

Figure 2. Colon transit times of the patients with chronic idiopathic constipation.

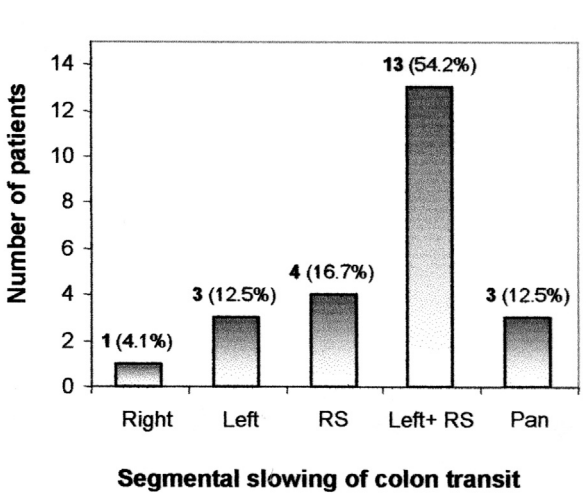

Figure 3. Segmental slowing of colon transit in patients with slow transit constipation (RS: Rectosigmoid, Pan: Pancolonic inertia).

transit time (CTT) with CTS and STC was observed in 24 of (64.8%) them. Characteristics of the patients with STC and normal transit constipation are shown in Table 1.

There were no significant differences between patients with STC and normal transit constipation in terms of age, sex, duration of constipation and defecation frequency ($p>0.05$).

The CTT was <72 hr in 13 (35.1%) patients (Figure 1a), 73-96 hr in six (16.2%) patients, 97-120 hr in 16 (43.2%) patients and >144 hr in two (5.4%) patients. There were no patients with a CTT of 121-144 hours (Figure 2).

Segmental slowing was observed at the right colon in one (4.1%) patient (Figure 1b), left colon in three (12.5%) (Figure 1c), pancolonic region in three (12.5%) (Figure 1d), rectosigmoid in four (16.7%) (Figure 1e) and left colon with rectosigmoid in 13 (54.2%) (Figure 1f) of the 24 patients with STC (Figure 3).

Gallbladder dysmotility (GBEF<40%) was observed in eight of 18 (44.4%) patients with STC (six patients with STC could not complete the study). Mean GBEF was 41.6±13.6% (16.3-67.0%) (Figure 4a and 4b).

The GBEF of the patients with STC according to the CTT is shown in Figure 5.

There was no significant quantitative correlation

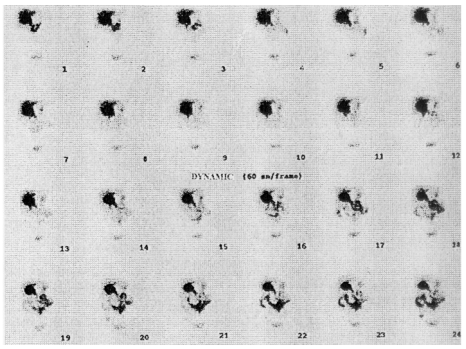

Figure 4a. Normal gallbladder ejection fraction (67.0%) measured by 99mTc-labeled trimethyl-3-bromo iminodiacetic acid (HIDA) cholescintigraphy.

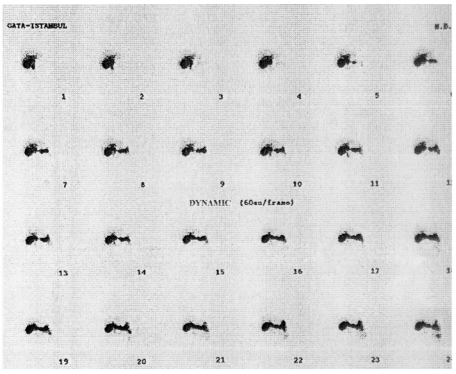

Figure 4b. Abnormal gallbladder ejection fraction (16.3%) measured by 99mTc-labeled trimethyl-3-bromo iminodiacetic acid (HIDA) cholescintigraphy.

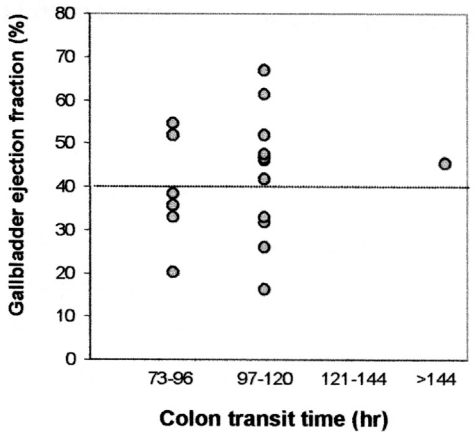

Figure 5. Gallbladder ejection fraction of the patients with slow transit constipation according to the colon transit time.

between the delaying of CTT and reduced GBEF (p=589, r=0.137).

Slowing of segmental gut transit was also not quantitatively correlated with decreased GBEF (p=0.387, r=0.417).

Patients with segmental slowing of the left colon and rectosigmoid region (being the most common form of segmental delaying in the study) had no significant correlation for CTT (p=0.531) and GBEF (p=1.00).

DISCUSSION

Symptoms of constipation may be caused by a variety of diseases and patients with constipation can be regarded as a heterogeneous group. Slow transit constipation has some characteristic features, such as predominance in young females, usual time of onset during childhood, unresponsiveness to bulk laxatives and stool-softeners, infrequent spontaneous defecations associated with abdominal discomfort, apparent normality of the colon and frequent association with other minor complaints related to hollow-organ dysfunction. The association of STC with gastrointestinal or urinary tract dysfunction or orthostatic hypotension and suggestions of a possible involvement of the autonomic nervous system have been reported by other authors (4, 12-14). There is increasing evidence that idiopathic STC is a distinct clinical entity comprising a pangastrointestinal motility disorder (7, 15). In this study, motility of the GB in patients with STC was evaluated with the use of scintigraphy and it was shown that these patients also have an abnormality of GB function.

A lower limit of normal of 40% for normal GB emptying was calculated using the mean±3 standard error of mean in a study of Yap et al. (11). On the basis of these criteria, eight of 18 (44.4%) patients with STC in the present study had an abnormally low GBEF. Mean GBEF was 41.6±13.6% (16.3-67.0%). We also demonstrated that delaying of both total and segmental CTT was not quantitatively correlated with decreased GBEF.

Neri et al. assessed the GB motor response to physiologic (sham feeding) and hormonal stimuli (intravenous infusion with gradually increasing doses of cholecystokinin (CCK)-analogue cerulein) in six patients affected by STC using USG (16). They showed a greater GB contraction in response to the meal and to cerulein.

Hemingway et al. screened patients with idiopathic STC to determine GB function by CCK-augmented HIDA scans (17). Eight of 10 patients in that study had low GBEF and median percentage EF of the scan was 28.5%. All 10 patients also had delayed solid phase gastric emptying.

In the study of Altomare et al., it was demonstrated that in the majority of patients with STC, motility disorders of the gastrointestinal tract (decreased gastric emptying 76%, delayed orocecal transit 90%, abnormal anorectal function 58%) and GB often coexist (18). Gallbladder motility was studied simultaneously with the use of USG and liquid test meal, and dysmotility (increased fasting, postprandial residual volume, or both) was observed in six of 14 patients (43%).

Delayed CTT and GB dysfunction may be linked to two findings. The increase in hepatic bile entering the proximal intestine could lead to greater exposure of bile salts to the anaerobic bacteria responsible for biotransformation of hydrophilic bile salts to more hydrophobic bile salts (19). Increase in these salts in the enterohepatic circulation might further impair GB motility because they have been shown to have a direct effect on the GB. The biliary proportion of hydrophobic deoxycholic acid has also been suggested to be greater in patients with constipation than in healthy subjects.

Defective GB emptying observed in patients with STC may also be secondary to altered postprandi-

al gastric emptying (18). This may be caused by a cologastric reflex produced by colonic distention rather than by an impairment of autonomic nerves.

In the study of Penning et al., GB emptying was studied (by USG) in response to neural, cephalic-vagal stimulation with modified sham feeding (MSF) and in response to hormonal stimulation with CCK (20). Their results showed that patients with STC have smaller fasting GB volumes, impaired GB responses to vagal cholinergic stimulation, but normal GB responses to hormonal stimulation with CCK. Reduced mean fasting GB volume may be influenced by CCK, but fasting plasma CCK concentrations of patients with STC were not different from those in control subjects. Also, reduced plasma peptide YY (induces relaxation of GB) concentrations may account for the reduction in fasting GB volume (21, 22). There was no correlation between individual body mass index and fasting GB volume. It is unlikely that small fasting GB volume is due to increased vagal tone because recent studies indicate that STC may be associated with autonomic neuropathy (12). Reduced GB contraction in response to MSF points to impaired vagal cholinergic transmission, which is in line with findings of parasympathetic autonomic neuropathy by Altomare et al (18). Abnormalities of the colonic myenteric plexus in STC might be another explanation for the impaired response of the GB to MSF (15).

The discrepancy in results between our study and those of Neri et al. (16), Hemingway et al. (17), Altomare et al. (18) and Penning et al. (20) may be related to patient selection, measurement techniques (scan versus USG), or infusion of CCK.

Demonstrating the presence of abnormal GB function in patients with STC supports the view that STC is a distinct clinical entity within the spectrum of severe constipation. Inclusion of the investigation of GB function in the work-up of patients with severe constipation may be beneficial and allow selection of this specific subgroup.

In conclusion, GB emptying is affected in patients with STC. Apart from the colon, the function of proximal gastrointestinal organs such as the GB is also affected in STC. Slow transit constipation may not be a purely colonic pathology but may be part of a generalized disorder of gastrointestinal motility which involves several gastrointestinal organs.

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