ORIGINAL ARTICLE

Gut and Liver, Vol. 9, No. 3, May 2015, pp. 388-394

Sonographic Evaluation of Gallbladder Motility in Children with Chronic Functional Constipation

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Background/Aims: Studies in adults suggest that constipation may not be a purely colonic pathology and may be a component of a generalized gastrointestinal (GI) motor disorder in which proximal GI motility can be impaired. Pediatric data are scarce, and the natural history of the disorder remains undefined. We aimed to evaluate gallbladder motility in a subset of Asian children with chronic functional constipation. **Methods:** Abdominal ultrasound was performed on 105 children, including 55 patients (aged 3 to 13 years) with chronic functional constipation who met the inclusion criteria and 50 age- and gender-matched controls. The gallbladder contractility index was calculated based on the preprandial and postprandial gallbladder areas. Preprandial and postprandial values for gallbladder volume and wall thickness were evaluated. **Results:** The mean value of the contractility index for the patients (15.77±24.68) was significantly lower than the mean value for the controls (43.66±11.58) ($p=0.001$). The mean postprandial gallbladder volumes and areas were larger in children with gallbladder hypomotility ($p<0.05$). The mean duration of constipation (4.8 months) was significantly higher ($p=0.004$) in the children with gallbladder hypomotility. **Conclusions:** Gallbladder motility is significantly impaired in children with chronic functional constipation. This study contributes to the understanding of the underlying pathophysiology, which will enable advancement in and improved management of children with chronic constipation and associated gallbladder hypomotility. **(Gut Liver 2015;9:388-394)**

Key Words: Constipation; Gallbladder; Motility; Ultrasound; Children

INTRODUCTION

Constipation is common in all age groups[1] and produces significant morbidity. In children, it accounts for 3% of referrals to pediatric outpatient clinics[2] and up to 25% of referrals to pediatric gastroenterology clinics.[3] In one-third of children, symptoms become chronic and may persist into adult life.[4,5]

Chronic constipation without any underlying structural, endocrine, or metabolic disease is termed functional or idiopathic constipation. The etiology of chronic functional constipation is largely unknown and is probably multifactorial. Slow transit constipation is one of the most common forms of chronic idiopathic constipation and is characterized by a lifelong history with no identifiable etiologic factor. It may be associated with impaired function of other gastrointestinal organs (stomach,[6] small bowel,[7] colon and anorectal function[8-10]).

Gallbladder dysmotility is identified in approximately half of patients with slow transit constipation.[11] Identification of the site of dysmotility in constipation may determine its causes and facilitate specific management. Also, constipated children may have gastroesophageal reflux more often than nonconstipated children.[12]

There are several imaging tests available to measure gallbladder contraction after a fatty meal, but it is still largely unknown whether the degree of contraction exhibited in a single study is reproducible and representative. Ultrasound is a well established safe, noninvasive technique for determining gallbladder volumes and for assessing gallbladder contraction. Unlike oral cholecystography and scintigraphy, sonography is quick and simple and there is no radiation exposure. There are studies on gallbladder motility in patients with constipation, but these reports are largely confined to the adult population.[13,14] There are strong indications that slow transit constipation (STC) in children and adults are distinct entities.[15,16]

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Received on November 6, 2013. Revised on December 29, 2013. Accepted on January 29, 2014. Published online on June 18, 2014
pISSN 1976-2283 eISSN 2005-1212 http://dx.doi.org/10.5009/gnl13414

Penning *et al*.[17] studied gallbladder emptying in adult population by ultrasonography in response to neural, cephalic-vagal stimulation and in response to hormonal stimulation with cholecystokinin; they found that fasting gallbladder volume was significantly reduced in patients with slow transit constipation compared with controls. However, postprandial gallbladder emptying was not evaluated. There is a single published study on gallbladder contractility in Brazilian children with chronic constipation by Veras Neto *et al*.[18] The authors identified gallbladder motility disorder in a subset of children with chronic constipation. Review of literature reveals that gallbladder motor function varies between different ethnic groups,[19] however the concept may hold true for all children.

To the best of our knowledge, there is no comprehensive study of gallbladder motility in Asian children with constipation. This research is an attempt to fulfill this gap and to test the hypothesis that a subset of children suffering from chronic functional constipation has associated gallbladder hypomotility.

MATERIALS AND METHODS

1. Study design

This prospective study was conducted on pediatric patients (ages ranging from 3 to 13 years) from the Asian subcontinent who had refractory functional constipation examined in the pediatric gastroenterology unit of our hospital after approval by our Institutional Thesis and Ethics Committee. The study included 55 patients with constipation and 50 healthy controls over a 2-year period (July 2010 to June 2012). The study was conducted in Departments of Gastroenterology & Radio Diagnosis. Informed consent was obtained from parents of all participants for the study.

2. Case group

The case group consisted of 55 patients in (ages ranging from 3 to 13 years) with refractory functional constipation. The children included were those with a ≥2 month history of at least two of the following symptoms as per the Paris Consensus on Childhood Constipation Terminology (PACCT) Group criteria:[20] (1) passage of hard and large-diameter stools; (2) discomfort or pain during faecal passage; (3) at least one episode of faecal incontinence per week; (4) defecation frequency <3 times/wk; (5) excessive straining and sensation of incomplete evacuation; and (6) presence of a palpable faecal mass and/or rectal fecal impaction. Children were excluded from the study if they had any known intestinal neuronal disease, renal or metabolic abnormalities, endocrine disorders (hypothyroidism), spinal or anal anomalies, history of any previous colon surgery, mental or motor disability, history of jaundice, billiary lithiasis, and drug usage other than laxatives.

3. Control group

The control group consisted of 50 clinically healthy children, age, and sex matched with the patients of the study group. They were selected from the group of children who came for regular immunization and surveillance procedures. Specifically, control children did not have any symptoms related to constipation or gastrointestinal complaint. Five selected children were excluded from the control group, because they did not accept the standard meal defined for the purpose of this study.

4. Gallbladder measurements

All cases and controls were subjected to ultrasonographic examination of the gallbladder after complete patient preparation. Twenty-four hours prior to ultrasonography, patients and controls were asked to refrain from using laxatives. Prior to being subjected to ultrasound examination, all patients and controls were fasted for at least 6 hours. All ultrasound examinations were done on a Philips HD 11XE (Philips Health Care, Bothell, WA, USA) ultrasound machine. All these studies were performed by the same operator using a 2- to 5-MHz convex transducer and the images were stored. Stored images were interpreted by two pediatric radiologists who were blinded to the clinical profile of these patients. The probe was placed obliquely in the right hypochondrium for better visualization of the gallbladder. The following measurements were recorded: (1) gallbladder wall (anterior) thickness (normal was defined when measuring up to 3 mm); (2) gallbladder volume (determined using Dodd's formula);[21,22] and (3) gallbladder area (calculated in cm^2 by the trace method). Transverse images were obtained at the site of maximal gallbladder width and longitudinal images through the long axis of the gallbladder. Area values were calculated automatically by selecting area trace, in both postprandial and preprandial states, after delimiting the maximal longitudinal ultrasonographic image of the gallbladder. Gallbladder volume was calculated by the ellipsoid method (Dodd's formula):

$$V=\prod/6\times(L\times W\times H)$$

Where L is the length, W is the width, and H is the height, or depth, of the gallbladder. The constant $\prod/6$ reduces to 0.52 (Figs 1-3).

Three measurements were recorded for each variable and averaged to provide a mean value for the fasting state and 1 hour (60 minutes) after ingestion of a defined standard meal containing 30 g of fat. Each child, regardless of age, was fed an Amul butter cube (30 g) and a single bread slice after consultation with the dieticians and as per the inclusion criteria of our study.

Based on the gallbladder area, the gallbladder contractility index (CI) was calculated using the following formula (average of three readings):

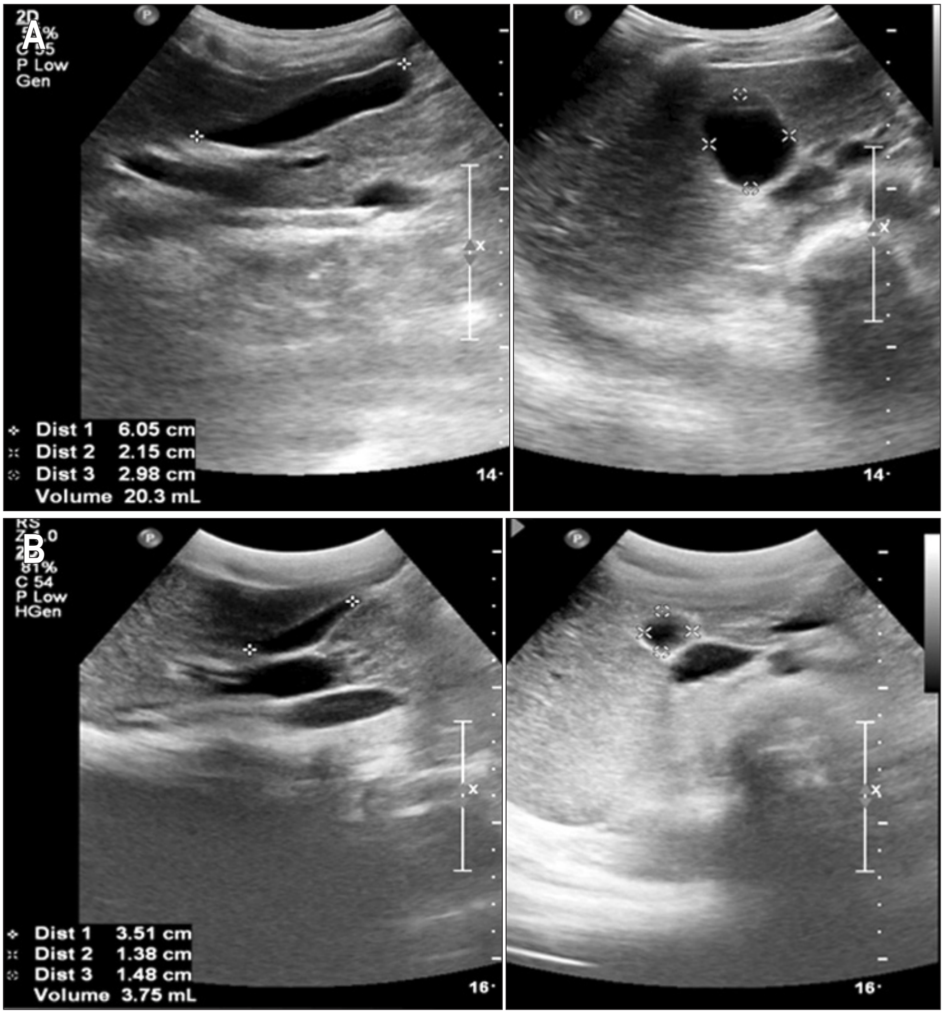

Fig. 1. Ultrasound evaluation of gallbladder volume using Dodd's formula in the preprandial (A) and postprandial (B) states in a control child. Distances 1, 2, and 3 represent gallbladder length, width, and height, respectively. The contractility index was 68.8%.

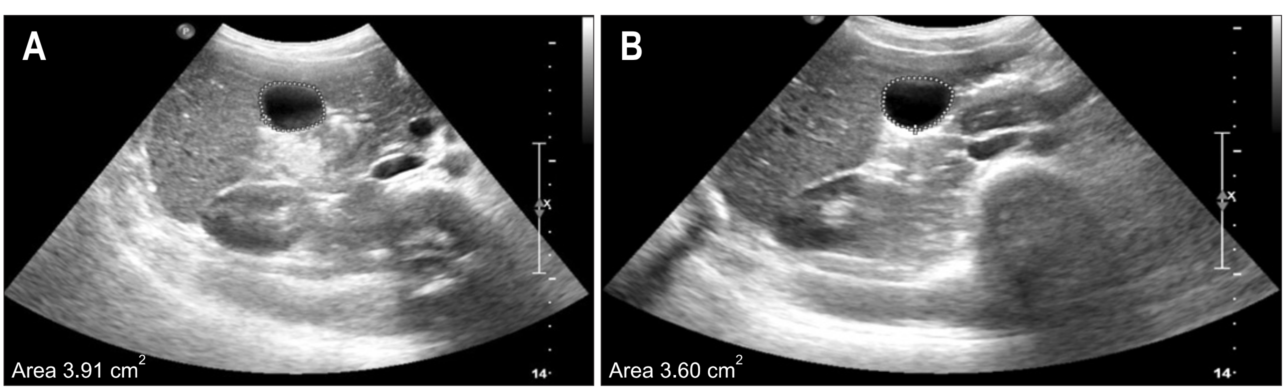

Fig. 2. Region-of-interest indicates the gallbladder cross-sectional area. Preprandial (A) and postprandial (B) ultrasounds in a 3-year-old child with constipation. The contractility index (CI) was 7.6% (CI, <25%).

$$CI\ (\%)=\{[\text{fasting gallbladder area } (cm^2)-\text{postprandial gallbladder area } (cm^2)]/\text{fasting gallbladder area}\}\times 100$$

A CI <25% was defined as hypomotility,[7-21] for the purpose of this study.

5. Statistical analysis

Logistic regression analysis was applied to control the effect of possible confounding variables (age, sex, and weight).

The mean, median, and standard deviation were calculated for the fasting and postprandial gallbladder areas, volumes and anterior wall thicknesses. To study the patient clinical data for possible associations with gallbladder hypomotility, the chi-square test was used. The chi-square was used to compare proportions between cases and controls. The Mann-Whitney test was used to compare CIs between cases and controls.

RESULTS

The mean age of the cases was 6.09 years (age range, 3 to 13 years) and for controls was 7.01 years (age range, 3 to 13 years), but there was no statistically significant association between age and gallbladder hypocontractility (p=0.95). However, gallbladder hypocontractility was more frequently observed in younger children (age <6 years) with an odds ratio of 1.014 and 95% confidence interval of 0.655 to 1.569. Similarly, there was no statistically significant association between sex distribution and gallbladder hypocontractility (p=0.45). The following symptoms were reported by 43 children in the case group: abdominal pain (n=21), fullness (n=7), early satiety (n=5), and abdominal distension (n=10). There was no statistically significant association between any of these symptoms (abdominal pain, p=0.89; fullness, p=0.77; early satiety, p=0.91; abdominal distension, p=0.86) and gallbladder hypomotility. The mean duration of constipation (4.8 months) was significantly higher (p=0.004) in the case group children than in children who had a CI >25%. The mean duration of constipation in this subset of children was (3.9 months). The mean body mass index (BMI) was 16.79 kg/m^2 in the cases and 18.66 kg/m^2 in the controls. Although the mean BMI of the controls was statistically higher than the mean value of the cases (p=0.01) (there was no statistically significant association between BMI and gallbladder hypomotility, p=0.11). However, there was a statistically significant association between the weight of the case children and gallbladder hypocontractility (p=0.03). The mean weight of the children with gallbladder hypomotility was significantly greater than children with normal gallbladder motility (22.1 kg vs 15.8 kg, p=0.03).

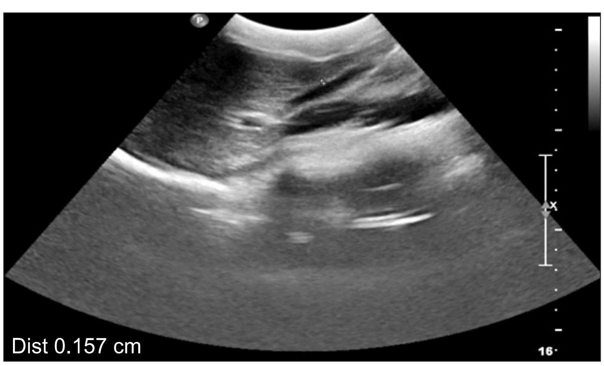

Fig. 3. Ultrasound evaluation of gallbladder wall (anterior) thickness.

With multivariate regression analysis, weight was an independent predictor of the gallbladder CI.

1. Statistical analysis of volume, area, and thickness

The mean preprandial volumes in the cases and controls were 6.73%±5.25 and 7.46%±4.46 cm^3, respectively. The mean preprandial area in the cases was 3.38±1.11 cm^2 and in the controls was 3.64%±1.60 cm^2. The preprandial areas were larger in the control group (Table 1). There was no statistically significant difference in preprandial values for the gallbladder volume, area and gallbladder hypomotility. Similarly there was no significant association between gallbladder wall thickness and hypomotility.

2. Statistics for the CI

The mean CI values for the cases and controls were 15.77%± 24.68% and 43.66%±11.58%, respectively. The Mann-Whitney test was applied and the mean CI value of cases was significantly lower than the mean value of the controls (p=0.001) (Table 2).

A total of 46 children had CI values <25%; 45 children from the case group and one child from the control group. A total of 59 children had CI values ≥25%; 10 were from the case group and 49 from the control group .The chi-square test was applied to compare the CI values (CI <25 or CI ≥25%) between cases

Table 1. Descriptive Values of Fasting and Postprandial Volumes, Areas, and Thicknesses in the Patient and Control Groups

Group	GB volume, cm^3		GB area, cm^2		GB thickness, mm	
	Fasting	Postprandial	Fasting	Postprandial	Fasting	Postprandial
Patients/cases						
No.	55	55	55	55	55	55
Mean±SD	6.7±5.2	5.3±4.1	3.3±1.1	2.6±1.9	1.4±1.1	1.4±1.1
Median	5.3	3.8	2.4	2.1	1.2	1.3
Controls						
No.	50	50	50	50	50	50
Mean±SD	7.4±4.4	4.3±3.0	3.6±1.6	2.0±0.9	1.2±0.2	1.3±0.7
Median	5.9	3.5	3.5	1.9	1.20	1.3
p-value*	0.18	0.25	0.03	0.2	0.1	0.37

GB, gallbladder.
*Mann-Whitney test.

Table 2. Contractility Indices in the Patients and Controls

Group	Contractility index, %	p-value
Cases (n=55)	15.7±24.6	0.001
Controls (n=50)	43.6±11.5	

Data are presented as mean±SD.

Table 3. Distribution of Contractility Indices <25% and ≥25% in the Patient and Control Groups

	Group		Total	Chi-square
	Cases	Control		
CI <25%				p=0.000
Count	45	1	46	
% Within group	81.8	2.0	43.8	
CI ≥25%				
Count	10	49	59	
% Within group	18.2	98.0	56.2	
Total				
Count	55	50	105	
% Within group	100.0	100.0	100.0	

CI, contractility index.

and controls. There was significant statistical association ($p<0.05$) between the cases and presence of a low CI (CI <25%) (Table 3). The odds ratio was calculated to estimate the risk. The risk of CI, <25% was approximately 5.7 times higher in the cases than the controls (odds ratio, 5.7; 95% confidence interval, 3.27 to 10.17).

DISCUSSION

Chronic constipation is a common ailment in children. Chronic idiopathic constipation caused by slow transit constipation is the most common forms of constipation, and is characterized by a lifelong history with no identifiable etiologic factor. Our study was designed to evaluate the association between chronic constipation and gallbladder hypomotility in children.

Our results show that gallbladder motility is significantly impaired in children with chronic functional constipation. Statistically significant association was found between the duration of constipation and gallbladder hypocontractility. The duration of constipation was more in children with CI less than 25%. Delayed colonic transit time and gallbladder dysfunction may be caused by the increase in hepatic bile entering the proximal intestine leading to greater exposure of bile salts to the anaerobic bacteria and thus transforming hydrophilic bile salts to more hydrophobic bile salts. Increase in these hydrophobic salts in the enterohepatic circulation might further impair gallbladder motility as they may have a direct effect on the gallbladder motility. There is increasing indication to suggest that idiopathic slow transit constipation is a distinct clinical entity comprising a pan-gastrointestinal motility disorder.[6-10] Günay *et al*.[14] used scintigraphy to evaluate whether motility in the gallbladder and stomach, were impaired in patients with slow transit constipation. Gallbladder dysmotility was observed in 44.4% of patients, and delayed gastric emptying was observed in 50% of patients. The authors described the presence of impaired gallbladder function in patients with slow transit constipation. This study further supports the hypothesis that slows transit constipation as a distinct clinical entity within the spectrum of severe constipation.

Gallbladder motility physiology is characterized by three different phases: a slow emptying which occurs immediately after ingestion of a meal, a second phase characterized by refilling, and a third that consists of a fast emptying.[23,24] The gallbladder is filled not only during fasting state but also during the postprandial period.[25,26] The gallbladder in healthy individuals is subject to temporary contractions and relaxations, related to food intake and the time of day.[27,28]

In our study, no significant association was observed between the age and sex of patients and controls and gallbladder hypomotility; however, younger (<6 years) was more frequently associated with gallbladder hypocontractility (CI <25%). These data may suggest that gallbladder motility disturbance may be an inherent phenomenon. Contractility indices for the constipated children (3 to 13 years) in our study were significantly lower than that of controls ($p<0.05$). The occurrence of a CI <25% was 5.7 times greater in cases compared to controls. These results are also consistent with a study in Brazilian (South American) population by Veras Neto *et al*.[18]

The presence of abnormal gallbladder motility in children with chronic constipation supports the hypothesis that slow transit constipation is a distinct clinical entity within the spectrum of severe constipation. Inclusion of the investigation of gallbladder function in the work-up of children with severe constipation may be beneficial and allow selection of this specific subset.

Our study also compared preprandial and postprandial values for gallbladder volume, area and thickness between cases and controls and explored the possibility of a statistical association with gallbladder hypomotility. There was no statistically significant difference in the mean gallbladder wall thicknesses and preprandial volumes between the patients and the control groups. The mean preprandial gallbladder areas were larger in control group. The postprandial volumes and area were significantly higher in children with gallbladder hypomotility. This finding may be explained by the complex gallbladder physiology. In the fasting state, the gallbladder undergoes partial emptying followed by refilling in conjunction with the migrating motor complex cycle of the small bowel. During the second half of the duodenal migrating motor complex cycle, the gallbladder contracts nearly 40%. Postprandial gallbladder contraction is characterized by an immediate cephalic phase regulated by excitatory cholinergic vagal nerves and a more prolonged phase generated by endogenous cholecystokinin. Apart from these factors, there are other factors like rate of gastric emptying and the amount of endogenous cholecystokinin release that may determine postprandial gallbladder emptying. The distal gut hormone peptide YY (PYY) induces relaxation of the gallbladder.[29] In patients with severe idiopathic constipation, reduced concentrations of plasma PPY have been found[30] and this may account for reduction in fasting gallbladder volume. Decreased gallbladder emptying observed in patients with slow transit constipation may also be secondary to impaired postprandial gastric emptying. This may be explained by a colo-gastric reflex produced by colonic distention.

The mean difference in the fasting and postprandial gallbladder volume and area values were lower in the patient group compared to controls, which was probably due to the significantly lower CI in the patients compared to controls ($p<0.05$). However, there was no significant difference in the preprandial and postprandial thicknesses between cases and controls.

There was no statistically significant association between the BMI and gallbladder hypomotility. However, in our study, there was significant association ($p<0.05$) between the mean weight of the cases and gallbladder hypocontractility (CI <25%). The weight of children who had CIs <25% was significantly greater as compared to children who had CI >25%. This may be because body habitus is also known to alter gallbladder dynamics, both obese and nonobese large people have significantly higher fasting gallbladder and residual gallbladder volumes with slower emptying rates than normal sized control subjects.[31] Multivariate regression analysis further confirmed that weight is an independent predictor of gallbladder hypocontractility. These findings may have important future consequences, which is supported by the findings of Pashankar *et al*.[31] who performed a retrospective review of 719 children, with chronic functional constipation between the ages of 4 to <18 years and they found a significantly higher prevalence of obesity in children with constipation compared to age- and gender- matched controls. However, longitudinal follow-up studies are needed to confirm these findings. In a recent study by Di Ciaula *et al*.,[32] the authors demonstrated gallbladder and gastric motility defects were associated with obesity in preadolescents and adults. The link between obesity and the risk of gallbladder disease seems to be secondary, at least in part, to insulin resistance,[33] a mechanism also most likely involving increased serum levels of leptin[34] and increased hepatic secretion of cholesterol.

Patients with chronic constipation frequently complain of dyspeptic symptoms, this may be explained by reflex inhibition of upper-gastrointestinal motor activity by colonic stimuli. In adults, the intermittent distension of the rectum at a level below that which caused any discomfort delayed the passage of a solid meal through both the stomach and the small intestine.[35] This cologastric brake may explain the upper-abdominal symptoms in constipated patients. The mechanism by which rectal distension inhibits gastric emptying probably involves both neural and humoral components.[36,37] Colonic loading with fecal materials may activate a rectogastric inhibitory reflex, altering the function of gastrointestinal tract regions proximal to the colon. This cologastric brake may account for the dyspeptic symptoms.

Our study has a few inherent limitations. Firstly, our study has a relatively small cohort size and also has a possible selection bias in the patient group. Also, sample size was not calculated statistically which can lead to possible errors. We enrolled 55 patients in study and 50 in control group prospectively, who met our inclusion criteria. Secondly, we have evaluated gallbladder motility only by real time ultrasound, which although is noninvasive and radiation free, can have subtle technical differences. Thirdly, we have not documented the actual transit time in these children with constipation. Slow transit constipation may only be a low gastrointestinal motility disorder, although we have stated that several studies suggest that idiopathic slow transit constipation may be a pangastrointestinal disorder.

As these were preliminary data, the CI after appropriate management of constipation was not determined. Nevertheless, follow-up surveys are ongoing at our center, and might provide relevant information in the future. Follow-up of these subset of children with chronic constipation in the future can reveal a temporary or chronic disorder.

Our study suggests that gallbladder motility is significantly impaired in children with chronic functional constipation and we propose performing motility investigations in children with constipation, to elicit the pathophysiological mechanism involved. Follow-up monitoring of these children with constipation in the future can reveal a temporary or chronic disorder. After the elimination of predisposing factors, changes in lifestyle, or the administration of proper treatment both pharmacologic and dietary there may be improvement in defecation, but it is still not clear if gallbladder motility will return to normal. To address this dilemma, more prospective studies with a higher number of cases should be performed in patients before and after appropriate management of constipation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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