Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective
Devanarayana, N.M.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 9

Ultrasonographic assessment of liquid gastric emptying and antral motility according to the subtypes of irritable bowel syndrome in children

This chapter of the thesis was published as

Devanarayana NM, Rajindrajith S, Bandara C, Shashiprabha G, Benninga MA

ABSTRACT

Objectives: Gastric motor abnormalities have been reported in adults with irritable bowel syndrome (IBS), commonly in constipation predominant IBS (IBS-C). However, such studies are uncommon in children. Furthermore, differences of gastric motility have not been studied in children with different IBS subtypes.

Methods: Seventy six children (33 [43%] males, age 4-14 years, mean 7.9 years, SD 3.0 years) fulfilling Rome III criteria for IBS and 20 healthy controls [8 (40%) males, age 4-14 years, mean 8.4 years, SD 3.0 years] were recruited (diarrhea predominant IBS [IBS-D]=21, IBS-C=31, mixed IBS [IBS-M]=19 and unsubtyped IBS [IBS-U]=5). Liquid gastric emptying rate (GER) and antral motility were assessed using an ultrasound method.

Results: Average GER (43.8% vs. 66.2% in controls), amplitude of antral contractions (A) (56.4% vs. 89.0%), and antral motility index (MI) (5.1 vs. 8.3) were lower and fasting antral area (FA) (1.6 vs. 0.6) was higher in patients with IBS (P<0.0001). Frequency of antral contractions (F) (8.9 vs. 9.3) did not show a significant difference. Patients exposed to stressful events had a significantly lower GER, compared to those not exposed to such events (P=0.03). Gastric motility parameters had no correlation with severity of symptoms.

GER (42.6%, 46.3%, 39.6%), FA (1.4 cm², 1.8 cm², 1.8 cm²), A (53%, 58.9%, 51.8%), F (8.7, 8.9, 9.2) and MI (4.7, 5.3, 4.8) were not different between IBS-D, IBS-C and IBS-M (P>0.05).

Conclusions: GER and antral motility parameters were significantly impaired in children with IBS compared to controls. GER and antral motility parameters were not different between IBS subtypes.
INTRODUCTION

Irritable bowel syndrome (IBS) in children is characterized by chronic abdominal pain relieved by defecation, and/or associated with changing frequency and/or form of stools. Prevalence of IBS varies from 5-14% in pediatric age groups in the western world and Asia.

The current understanding of pathophysiology of IBS is based on studies conducted in adults. Pediatric studies assessing pathophysiological mechanisms in IBS are rare. Gastric motor abnormalities such as delayed gastric emptying have been reported in adult patients with IBS. However, some of these studies have reported such abnormalities only in patients with constipation predominant IBS and those with dyspepsia. This led to the belief that gastric motility abnormalities in IBS occur as a result of activated colo-gastric reflex and/or concurrent functional dyspepsia. Lack of correlation with symptoms has further diminished the importance of gastric motor abnormalities in pathogenesis of this condition. In contrast to adults however, the predominant symptom in children with IBS is abdominal pain. Abnormalities of gastric motility such as antral hypomotility and delayed gastric emptying have been reported in several pediatric disorders, in which the predominant symptom is abdominal pain (e.g. functional dyspepsia [FD], functional abdominal pain and recurrent abdominal pain of functional origin). In several of these studies, there was a significant correlation between symptom severity and reduction in gastric emptying, indicating a possible pathophysiological role. Detailed studies on gastric motility and its relationship with symptoms are not available in children with IBS. Furthermore, differences in gastric motility in different IBS subtypes (constipation predominant [IBS-C], diarrhea predominant [IBS-D], mixed [IBS-M] and unsubtype [IBS-U] IBS) have not been studied previously.

Exploration of pathogenesis of IBS is of utmost importance in order to define treatment strategies for this common and troublesome disease condition in children. In this study, we studied gastric emptying and antral motility abnormalities in children with IBS and assessed their relationship with IBS subtypes and symptoms.

MATERIALS AND METHODS

Patients

Between January 2007 and December 2011, children referred to the gastroenterology research laboratory of a tertiary care hospital in Sri Lanka, and fulfilling the Rome III criteria for IBS were included in this study. All of them had been screened for organic diseases using history, physical examination, complete blood count, C-reactive protein, liver and renal function tests, urine microscopy and culture and stool microscopy. Specific investigations performed in some
patients based on clinical judgment included abdominal ultrasound ($n=23$), barium contrast studies ($n=3$), lower gastrointestinal endoscopy ($n=4$), upper gastrointestinal endoscopy ($n=1$) and X-ray KUB ($n=5$). None had clinical or laboratory evidence of organic diseases. In this study, IBS was diagnosed using standard Rome III criteria for children and adolescents. Furthermore, demographic data, pain severity and exposure to emotional stress were recorded. A parent or a legally accepted guardian had given informed consent to carry out gastric motility studies.

Rome III criteria for IBS

Abdominal discomfort or pain that occurs at least once per week for more than two months, and associated with at least two of the following three features for at least 25% of the time;

- abdominal pain improved with defecation
- onset associated with change in stool frequency
- onset associated with a change in consistency of stools.

Recruited children were divided into IBS subtypes as follows,

- Constipation predominant IBS - hard or lumpy stools $\geq 25\%$ and loose (mushy) or watery stools $< 25\%$ of bowel movements
- Diarrhea predominant IBS - loose (mushy) stools or watery stools $\geq 25\%$ and hard or lumpy stools $< 25\%$ of bowel movements
- Mixed IBS – hard or lumpy $\geq 25\%$ and loose (mushy) or watery stools $\geq 25\%$ of bowel movements
- Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D or IBS-M.

Severity of symptoms was recorded using a four point scale.

1 - child is able to carry out regular activities during pain episodes
2 - child stops all activities and sits down during pain episodes
3 - child lies down during pain episodes
4 - child cries or screams during pain episodes

Selection of controls

Twenty healthy children age 4-14 years without gastrointestinal symptoms were recruited as controls. Written consent has been obtained from parent or guardian of all controls. These controls were also described in a previous study.
**Assessment of gastric emptying and antral motility**

The main gastric motility parameters assessed in the current study were gastric emptying rate and antral motility (frequency of antral contractions, amplitude of antral contractions and antral motility index). Gastric motility was assessed using a previously reported non-invasive, ultrasound method.\(^\text{17,18}\) All assessments were performed using a real-time ultrasound scanner with a 3.5 MHz curve linear transducer (SD-550, Aloka, Tokyo, Japan). All motility assessments were performed between 8.30 am and 9.00 am. The ultrasound probe was positioned vertically on the anterior abdomen to permit simultaneous visualization of the antrum, left lobe of liver, superior mesenteric artery and abdominal aorta. The gastric antral area was measured using the built in caliper and tracing the mucosal side of the wall. For the assessment of gastric emptying, antral cross sectional area was measured during fasting period and during 1 min and 15 min after drinking a test meal (200 mL of chicken soup, 54.8 kJ, 0.38 g protein, 0.25 g fat, 2.3 g sugar per serving, heated to approximately 40°C, consumed with in 2 min) (Figure 8.1). For assessment of amplitude of antral contractions, the antral area was measured during three consecutive contractions and relaxations. The frequency of antral contractions was calculated for a period of 3 min. Antral motility parameters were calculated within the first 5 min after the meal.\(^\text{17,18}\) The same experienced investigator performed all ultrasound examinations.

![Figure 8.1 - Ultrasound assessment of gastric emptying rate](image)

**A** – antral cross sectional area at 1 min, **B** – antral cross sectional area at 15 min

Gastric emptying and antral motility were calculated as follows:

- **Gastric emptying** = \( \frac{[\text{Antral area at 1 min} - \text{Antral area at 15 min}]}{\text{Antral area at 1 min}} \times 100 \)
- **Frequency of antral contractions** = Number of contractions per 3 min
• Amplitude of contractions = [Antral area at relaxation – Antral area at contraction] /Antral area at relaxation X 100
• Motility index = [Amplitude of antral contraction X Frequency of contraction]/100

**Statistical analysis**
Gastric motility parameters of patients and controls and between IBS subtypes were compared using the Mann–Whitney U-test. Gastric motility parameters and symptom scores were correlated using Spearman Correlation Coefficient. A P value of 0.05 or less was considered statistically significant.

**Ethical approval**
The ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

**RESULTS**
Seventy six children fulfilling the Rome III criteria for IBS (33 [43%] males, age 4-14 years, mean 7.9 years, SD 3.0 years) were included in this study. They were categorized into IBS-D (n=21), IBS-C (n=31), IBS-M (n=19) and IBS-U (n=5) according to Rome III criteria. Twenty healthy children (8 [40%] males, age 4-14 years, mean 8.4 years, SD 3.0 years) were recruited from the same area as controls.

**Gastric motility parameters in patients and controls**
Table 9.1 demonstrates the gastric motility parameters in children with IBS and controls. Gastric emptying rate and antral motility index were significantly impaired in children with IBS compared to controls. No significant difference observed in gastric motility parameters between different IBS subtypes.

**Relationship between gastric motility parameters and symptoms**
Table 9.2 shows the correlation between motility parameters and severity of symptoms. No significant correlation observed between severity of symptoms and motility parameters.

Gastric emptying rate in IBS patients with nausea (n=20, 26.3%) and those without nausea were respectively 40.4% and 45.1% (P=0.21, unpaired t test). There was no significant difference in gastric motility parameters in patients with IBS who had dyspepsia (n=12, 15.8%), compared to those without dyspepsia (Table 9.3).
Table 9.1 – Gastric motility in children with IBS and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>IBS-D (n=21) Mean (SD)</th>
<th>IBS-C (n=31) Mean (SD)</th>
<th>IBS-M (n=19) Mean (SD)</th>
<th>IBS-U (n=5) Mean (SD)</th>
<th>IBS-total (n=76) Mean (SD)</th>
<th>Controls (n=20) Mean (SD)</th>
<th>IBS-total vs. controls P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm²)</td>
<td>1.4 (1.0)</td>
<td>1.8 (1.5)</td>
<td>1.8 (1.0)</td>
<td>0.9 (0.7)</td>
<td>1.6 (1.2)</td>
<td>0.6 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>42.6 (14.6)</td>
<td>46.3 (12.6)</td>
<td>39.6 (16.4)</td>
<td>50.5 (14.5)</td>
<td>43.8 (14.4)</td>
<td>66.2 (16.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>53.0 (14.0)</td>
<td>58.9 (18.7)</td>
<td>51.8 (11.5)</td>
<td>72.9 (14.5)</td>
<td>56.4 (16.3)</td>
<td>89.0 (10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of antral contractions (/3min)</td>
<td>8.7 (1.0)</td>
<td>8.9 (1.4)</td>
<td>9.2 (1.0)</td>
<td>8.4 (1.5)</td>
<td>8.9 (1.2)</td>
<td>9.3 (0.8)</td>
<td>0.159</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>4.7 (1.5)</td>
<td>5.3 (2.1)</td>
<td>4.8 (1.2)</td>
<td>6.0 (0.5)</td>
<td>5.1 (1.7)</td>
<td>8.3 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Mann Whitney U test
Table 9.2 – Relationship between gastric motility parameters and severity of symptoms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Correlation*</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm(^2))</td>
<td>0.041</td>
<td>0.73</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>0.086</td>
<td>0.46</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>-0.107</td>
<td>0.36</td>
</tr>
<tr>
<td>Frequency of antral contractions (/3min)</td>
<td>-0.096</td>
<td>0.42</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>-0.174</td>
<td>0.13</td>
</tr>
</tbody>
</table>

*Spearman correlation coefficient

Table 9.3 – Association between dyspepsia and gastric motility in children with IBS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dyspepsia present ((n=12)) mean (SD)</th>
<th>Dyspepsia absent ((n=68)) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm(^2))</td>
<td>1.6 (1.1)</td>
<td>1.6 (1.3)</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>43.2 (8.9)</td>
<td>44.0 (15.2)</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>55.8 (11.3)</td>
<td>56.5 (17.1)</td>
</tr>
<tr>
<td>Frequency of antral contractions (/3min)</td>
<td>8.7 (1.2)</td>
<td>8.9 (1.2)</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>4.8 (1.2)</td>
<td>5.1 (1.8)</td>
</tr>
</tbody>
</table>

\(P>0.05\) for all comparisons between two groups, Mann Whitney U test

**Association between gastric motility and exposure to stressful events**

Fifty children with IBS (65.6%) and 6 controls (30%) were exposed to at least one family or school related stressful life events during previous 3 months. The common stressful life events recognized by the children with IBS were preparation for the grade 5 scholarship examination (\(n=18\)), father or mother working abroad (\(n=14\)), disharmony in the family and frequent domestic fights (\(n=13\)), hospitalization of the child him/herself for other illness (\(n=10\)) and frequent punishment at school (\(n=10\)). Gastric motility parameters in children exposed to stressful events and not exposed to such events are shown in Table 9.4. Children with IBS exposed to stressful life events had significantly delayed gastric emptying compared to those not exposed to such event.
Table 9.4 – Association between exposure to stressful life events and gastric motility in children with IBS

<table>
<thead>
<tr>
<th></th>
<th>Exposed to stressful events (n=50) mean (SD)</th>
<th>Not exposed to stressful events (n=26) mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm²)</td>
<td>1.8 (1.6)</td>
<td>1.5 (1.0)</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>40.3 (16.9)*</td>
<td>45.7 (12.6)</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>56.1 (16.7)</td>
<td>56.6 (16.1)</td>
</tr>
<tr>
<td>Frequency of antral contractions (/3min)</td>
<td>8.8 (1.7)</td>
<td>8.9 (0.9)</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>4.9 (1.8)</td>
<td>5.1 (1.7)</td>
</tr>
</tbody>
</table>

*P<0.029, Mann Whitney U test

DISCUSSION

For the first time, this study has compared gastric motility in all four subtypes of irritable bowel syndrome in children. In this study we found significantly lower gastric emptying and antral motility in all four subtypes of IBS compared to controls. There was no difference in gastric emptying rate and antral motility parameters between IBS subtypes. Children with IBS, who were exposed to recent stressful life events, had a significantly lower gastric emptying rate.

We have used a simple, safe and non-invasive ultrasound method to measure liquid gastric emptying which has been previously used in children with functional gastrointestinal disorders. In addition, ultrasound methods of assessing gastric emptying have shown a good interobserver agreement,19 and closely correlate with scintigraphic assessment of gastric emptying which is considered as the gold standard.20 Liquid gastric emptying is reported to be abnormal in patients who have normal gastric emptying for solids, and is considered to be more sensitive to detect gastroparesis in non-diabetic patients.21-23 Furthermore this method allows us to measure the antral motility and the fasting antral area which are also important parameters of gastric motor function.

This study showed that liquid gastric emptying measured in a cohort of children with IBS was significantly lower than that of healthy controls. Even though, there are no previously published studies assessing gastric motility in children with IBS, delayed gastric emptying have been
reported in children with other abdominal pain predominant disorders such as functional dyspepsia (FD), functional abdominal pain and recurrent abdominal pain of functional origin. Previous studies conducted in adult patients with IBS have reported contradicting results. While several studies have shown significantly delayed gastric emptying in patients with IBS compared to controls, another study has failed to demonstrate such a difference. Small sample size of the latter study might have contributed to this lack of difference.

In addition to gastric emptying, antral motility parameters (both frequency and amplitude of contraction) were also significantly lower in children with IBS in this study. Even though not reported in children with IBS, impaired antral motility is a common feature in both children and adults with functional dyspepsia, functional abdominal pain and recurrent abdominal pain. Impaired antral motility is probably the main contributor for delayed gastric emptying observed in children with abdominal pain predominant functional gastrointestinal diseases. A previous study has reported a significant correlation between gastric emptying rate and antral motility index in children with FAP.

In this study we found a higher antral area during fasting period in children with IBS. A similar result has been reported in functional abdominal pain and functional dyspepsia. However, a previous study conducted in adult patients with IBS failed to demonstrate a significant difference in fasting antral size. A wide gastric antrum found upon ultrasonography correlates with the amount of liquid retained in the stomach. Indeed children with IBS in this study retain more liquids during fasting period. An exact reason for this phenomenon is not clear, but this may possibly be due to ineffective migrating motor complexes causing poor gastric clearance and accumulation of gastric secretions in the distal stomach. In agreement with this, a previous study has reported abnormalities in small intestinal migrating motor complexes in children with recurrent abdominal pain.

For the first time, we compared gastric motility in children with different IBS subtypes. Children with all four subtypes of IBS had impaired gastric emptying rates and antral motility parameters compared to controls, and there was no significant difference between different IBS subtypes. Similarly, Nielsen and colleagues did not find a significant difference in gastric emptying times in adult patients with IBS-D and IBS-C, even though patients with IBS-D had faster small intestinal transit than those with IBS-C. Similarly, another adult study using Rome II criteria has reported delayed gastric emptying in 26% of IBS-C, 21% of IBS-D and 18% in IBS with alternating bowel habits (IBS-M). In contrast to these, a previous study using radio-labeled technetium-99m demonstrated a significantly lower gastric emptying for solids in adults with
IBS-C than in IBS-D. However, in this study gastric emptying for liquids and indigestible solids were similar in both sub-groups which is compatible with our results.

We did not observe a significant correlation between gastric motility parameters and severity of symptoms. Similar results have been reported in adult patients with IBS. However, two previous studies conducted in Sri Lankan children with recurrent abdominal pain and functional abdominal pain have reported significant negative correlations between severity of abdominal pain and gastric emptying rate. In contrast to previous studies, where the majority of subjects suffer from abdominal pain only, children with IBS recruited in the current study had symptoms related to defecation. Therefore, symptoms may not be completely of gastric origin, but also related to lower gastrointestinal tract. This may be the reason for lack of correlation between gastric motility and symptom severity.

The exact cause for decreased gastric motility in children with IBS is not clear. Presence of concurrent functional dyspepsia is commonly suggested as a possible reason for abnormal gastric motility observed in patients with IBS. However, the relationship between dyspeptic symptoms and delayed gastric emptying in patients with IBS is controversial. Stanghellini et al. reported a significant association between delayed gastric emptying and overlapping postprandial fullness and nausea, while Portincasa et al. failed to find such an association. Unlike adult patients with IBS, only 15.8% children recruited in this study had dyspeptic symptoms including epigastric pain, epigastric fullness, bloating and early satiety. Furthermore, in contrast to previous adult studies, we did not observe a significant difference in gastric motility parameters in IBS patients with dyspepsia compared to those without dyspepsia.

In addition, activation of colo-gastric reflex has been suggested as a possible reason for delayed gastric emptying in patient with IBS, since several adult studies have reported delayed gastric emptying in patients with chronic constipation and constipation associated IBS. Another study, conducted in adult patients with dyspepsia, has demonstrated delayed gastric emptying in most patients with overlapping constipation and also a significant improvement in gastric emptying following administration of osmotic laxatives. However, in contrast to those previous studies, decreased gastric emptying and antral motility observed in our patients with IBS are unlikely to be due to constipation and colo-gastric reflex since those with IBS-D, IBS-M and IBS-U also had similar gastric motility abnormalities to that of those with IBS-C. Therefore, the gastric motor abnormalities present in children with IBS seem to be of more complex in origin than previously believed and future studies are needed to explore these pathophysiological mechanisms.
Irritable bowel syndrome and other FGIDs in children are frequently associated with psychological factors. Several studies in children with abdominal pain have reported higher prevalence of recurrent abdominal pain, abdominal pain predominant FGIDs and constipation in those exposed to stressful life events.\textsuperscript{5,31-33} It has been postulated that, in genetically vulnerable individuals, sustained stress can result in persistent increase in responsiveness of central stress circuits. This predisposes such individuals to develop functional gastrointestinal diseases. Emotional stress is important in altering brain-gut interactions resulting in development and exacerbation of IBS symptoms.\textsuperscript{34} Emotional stress can significantly influence gut motility,\textsuperscript{35} secretion and mucosal immunological functions,\textsuperscript{36} through the brain-gut axis. However the association between emotional stress and gastric motility has not been studied in children with IBS. Previous studies conducted in children with FAP and recurrent abdominal pain, have failed to demonstrate an association between exposure to stressful events and gastrointestinal motility.\textsuperscript{14,15} In this study, the majority of children with IBS were exposed to at least one stressful event during previous 3 months. For the first time, we found a significantly lower gastric emptying in children with IBS, who were exposed to stressful life events. Our findings give evidence on the influence of psychological factors on gastric motility through the brain-gut axis.

In conclusion, the gastric emptying rate and antral motility parameters were significantly impaired in Sri Lankan children with IBS. Furthermore, children with all four IBS subtypes had delayed gastric emptying and impaired antral motility. However, we failed to demonstrate a clear relationship between symptoms and motility abnormalities. Children exposed to recent stressful life events had a significantly lower gastric emptying rate compared to those not exposed to such events, suggesting the possibility of altered brain-gut interactions in the pathogenesis of IBS. The therapeutic value of psychotherapies, which target on reducing stress and anxiety, and gastro-prokinetic drugs, which improve of gastric motility, are needed to be explored further in management of IBS.

REFERENCES


