Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective

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Chapter 8

Delayed gastric emptying rates and impaired antral motility in children fulfilling Rome III criteria for functional abdominal pain

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ABSTRACT

Background: Gastric sensorimotor dysfunctions have been implicated in the pathophysiology of some functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome. Therefore, we hypothesized that abnormal gastric emptying and impaired antral motility are possible underlying mechanisms of symptoms in children with functional abdominal pain (FAP).

Methods: Hundred and two children (37 [36.3%] males, 4-14 years, mean 7.8 years, SD 2.7 years) fulfilling Rome III criteria for FAP were recruited for this study. An age and sex compatible group of healthy children (n=20) were selected as controls (8 [40%] males, 4-14 years, mean 8.4 years, SD 3.0 years). Liquid gastric emptying rate (GER) and antral motility parameters (amplitude of antral contractions, frequency of antral contractions and antral motility index) were assessed using a previously reported ultrasound method.

Results: Average GER (42.1% vs. 66.2% in controls), amplitude of antral contractions (56.5% vs. 89.0%), frequency of contractions per 3 min (8.5 vs. 9.3) and antral motility index (4.9 vs. 8.3) were significantly lower in patients with FAP compared to controls (P<0.01). Fasting antral area was higher in patients (1.4 vs. 0.6, P<0.0001). GER negatively correlated with the scores obtained for severity of abdominal pain (r=-0.29, P=0.004).

Conclusions: GER and antral motility parameters were significantly impaired in patients with FAP and GER negatively correlated with symptom severity. These findings highlight the possible role of gastrointestinal motility abnormalities in the pathophysiology of childhood FAP.
INTRODUCTION

Recurrent or chronic abdominal pain is a global health problem affecting 10-12% of school aged children, but only less than 25% of affected children have identifiable cause for their symptoms. More than 75% of children with recurrent abdominal pain suffer from functional gastrointestinal disorders (FGIDs) of which functional abdominal pain (FAP) is the commonest. In community based studies, FAP is seen in 3.0% of school aged children.

Exact cause for pain is unclear in children with FGIDs. The typical periumbilical pain, present in the majority of children with FAP, is suggestive of visceral pain of gastrointestinal origin. Putative pathophysiological mechanisms for the pain include enhanced visceral sensitivity and gastrointestinal motility abnormalities. Gastrointestinal motility has been previously assessed in children and adults with FGIDs such as functional dyspepsia (FD) and irritable bowel syndrome (IBS). These studies have reported delayed gastric emptying for liquid and solids, impaired proximal stomach accommodation, abnormal antral motility and wide gastric antrum during fasting period.

In contrast to FD and IBS, FAP has received little attention from researchers. Due to this, very little is known regarding motility abnormalities and their clinical significance in children with FAP whose predominant symptom is abdominal pain. Therefore, this retrospective study was conducted with the aim of looking at the abnormalities in gastric emptying and antral motility in children with FAP and the relationship between gastric motility abnormalities and clinical symptoms.

MATERIALS AND METHODS

This is a retrospective study conducted in children referred to the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, during 5 year period from 1st January 2006 to 31st December 2010.

Ethical approval

This study protocol was approved by the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka.

Selection of patients

All children age 4 to 14 years who have undergone gastric motility assessments in Gastroenterology Research Laboratory for diagnostic purposes were screened. Children who fulfilled Rome III criteria for FAP were selected and included in this study.
Rome III criteria for FAP are as follows.
Abdominal pain once per week for at least 2 months with all of the following features,

- Episodic or continuous abdominal pain
- Insufficient criteria for other functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject’s symptoms

**Screening for organic disorders**
All patients recruited had been screened for organic disorders using rigorous history and comprehensive physical examination (including growth parameters) to exclude any other plausible explanation for abdominal pain. Routine investigations done in all recruited patients to rule out organic disorders, included stool microscopy, urine microscopy and culture, full blood count, C-reactive protein, liver and renal function tests. Special investigations performed in some patients based on clinical judgment included ultrasound scanning of the abdomen \((n=54)\), X-ray KUB \((n=32)\), serum amylase \((n=4)\), upper gastrointestinal endoscopy \((n=4)\), lower gastrointestinal endoscopy \((n=1)\) and barium enema \((n=3)\).

**Symptom severity**
Severity of abdominal pain was graded as mild (1 – child is able to carry out regular activities during pain episodes), moderate (2 – child stops activities and sits down during pain episodes), severe (3 – child lies down during pain episodes) and very severe (4 – child cries or screams during pain episodes). The patients were followed up for a minimum of 6 months.

**Exclusion criteria**
- Clinical or laboratory evidence suggesting organic pathology
- Functional gastrointestinal disorders other than FAP
- Chronic medical or surgical disease other than FAP
- Long-term medication for any illness other than FAP
- Previous abdominal surgery involving gastrointestinal tract except appendectomy
- Fever, common cold, respiratory tract symptoms, gastroenteritis or any other systemic infection during the previous month
- Subjects receiving prokinetic drugs or any other drugs that can alter gastrointestinal motility during the previous month
Selection of controls

Twenty healthy children aged 4-14 years, without symptoms related to the gastrointestinal tract (e.g. abdominal pain, abdominal distension, constipation, diarrhea etc.), were recruited as controls after obtaining written consent from a parent. Eighteen of the controls were also included in a previous study published in 2008.16

Laboratory methods

Gastric emptying rate and antral motility were evaluated with real-time ultrasonography by using previously reported and validated method.13 All subjects underwent measurement of gastric emptying by a high-resolution, real-time scanner with a 3.5MHz curve linear transducer. The same investigator (NMD) performed all ultrasound examinations.

Calculation of liquid gastric emptying rate

After an overnight fast, study subjects were examined seated in a chair leaning slightly backwards. The cross sectional area of antrum was calculated in the fasting stage and after drinking a standard liquid meal heated to approximately 40°C within 2 min (200mL of chicken soup, 54.8kJ, 0.38g protein, 0.25g fat, 2.3g sugar per serving, Ajinomoto Co., Tokyo, Japan). The ultrasound probe was positioned vertically to permit simultaneous visualization of gastric antrum, superior mesenteric artery, abdominal aorta and the left lobe of liver (Figure 8.1). The area of gastric antrum was measured by tracing the mucosal side of the wall using the built-in caliper and calculation program of the ultrasound apparatus. Antral cross sectional area was measured at 1min and 15min after drinking the test meal. Gastric emptying rate was calculated as the percentage reduction of gastric antral cross sectional area at 15min following ingestion of the liquid meal.

\[
\text{Gastric emptying rate (\%) = \frac{\text{Antral area at 1min} - \text{Antral area at 15min}}{\text{Antral area at 1min}} \times 100}
\]
Calculation of antral motility
These antral motility parameters were calculated within first 5 minutes after drinking the liquid meal. The minimum and maximum cross sectional areas of the antrum were measured during contractions and relaxations for at least 3 times to calculate the amplitude of antral contractions.

Antral motility parameters were calculated as follows:
Frequency of antral contractions = Number of contractions per 3 min
Amplitude (%) = \( \frac{\text{Antral area at relaxation} - \text{Antral area at contraction}}{\text{Antral area at relaxation}} \times 100 \)
Motility index = Amplitude of antral contraction \( \times \) Frequency of contraction

Statistical analysis
The data were analyzed using EpilInfo (EpiInfo 6, version 6.04 (1996), Centers of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). The statistical significance of differences of gastric motility parameters between the patient and control groups were assessed using Mann-Whitney U-test. Spearman correlation coefficient was used to assess the relationship between gastric emptying parameters and severity of abdominal pain.
RESULTS

Gastric motility data of 102 children with FAP (37 [36.3%] boys, age 4-14 years, mean 7.8 years, SD 2.7 years) and 20 healthy controls (8 [40%] boys, age 4-14 years, mean 8.4 years, SD 3.0 years) were analyzed. Abdominal pain characteristics of the study population are summarized in Table 8.1.

Table 8.1 – Abdominal pain characteristics in children with FAP

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td>6.7</td>
<td>2.5-14.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Duration of FAP (months)</td>
<td>12.9</td>
<td>2-72</td>
<td>14.9</td>
</tr>
<tr>
<td>Frequency of pain episodes (episodes/month)</td>
<td>30.1</td>
<td>4-240</td>
<td>34.4</td>
</tr>
<tr>
<td>Duration of a pain episode (hours)</td>
<td>1.31</td>
<td>0.05-24</td>
<td>4.2</td>
</tr>
<tr>
<td>Abdominal pain severity score</td>
<td>2.5</td>
<td>1-4</td>
<td>0.9</td>
</tr>
</tbody>
</table>

FAP=Functional abdominal pain

Gastric motility parameters of patients and controls

Children with FAP had significantly lower gastric emptying rate, frequency and amplitude of antral contractions and antral motility index. Furthermore, their fasting antral area was significantly higher than that of controls (Table 8.2).

Figure 8.2 shows the gastric emptying rates of patients and controls according to age. The majority (42 [55.3%]) of affected children had gastric emptying rates below the 10th percentile of that of controls.

Furthermore, gastric emptying rate had a significant negative correlation (r= -0.29) with the scores obtained for severity of abdominal pain (Table 8.3).

Association between emotional stress and gastric motility

A total of 59 (57.8%) children have been exposed to at least one school and family related stressful life events during the previous 3 months. When patients with FAP who were exposed to stressful events were compared with those not exposed to such events, fasting antral area (1.5 cm² [SD 1.3 cm²] vs. 1.2 cm² [SD 1.0 cm²] in controls), mean gastric emptying rate (40.3% [SD 17.6%] vs. 44.5% [SD 15.6%]), mean amplitude of antral contractions (56.2% [SD 17.0%] vs. 56.9% [SD 17.0%]), frequency of antral contraction per 3 min (8.4 [SD 1.4] vs. 8.8 [SD 0.7])

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and antral motility index (4.8 [SD 1.8] vs. 5.0 [SD 1.7]) were not significantly different between two groups ($P>0.05$, Mann-Whitney U test).

**Table 8.3 – Correlation between abdominal pain characteristics and gastric emptying in children with FAP**

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Correlation coefficient</th>
<th>95% confidence interval</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of abdominal pain (episodes/week)</td>
<td>-0.07</td>
<td>-0.258 to 0.129</td>
<td>0.506</td>
</tr>
<tr>
<td>Scores obtained for severity of abdominal pain</td>
<td>-0.29</td>
<td>-0.455 to -0.097</td>
<td>0.004</td>
</tr>
<tr>
<td>Average duration of a pain episode (min)</td>
<td>-0.03</td>
<td>-0.223 to 0.165</td>
<td>0.765</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>0.03</td>
<td>-0.164 to 0.224</td>
<td>0.757</td>
</tr>
<tr>
<td>Age at onset of the disease (years)</td>
<td>-0.05</td>
<td>-0.240 to 0.148</td>
<td>0.633</td>
</tr>
</tbody>
</table>

*Spearman’s correlation coefficient

**Figure 8.2 – Gastric emptying rates in patients and controls according to age**

Reference lines are 10th and 90th percentiles of gastric emptying rates for healthy controls.
### Table 8.2 – Gastric motility parameters in children with FAP and controls

<table>
<thead>
<tr>
<th>Gastric motility parameter</th>
<th>Children with FAP</th>
<th>Healthy controls</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm²)</td>
<td>1.4</td>
<td>0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>42.1</td>
<td>66.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>56.5</td>
<td>89.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of antral contraction (per 3 min)</td>
<td>8.5</td>
<td>9.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>4.9</td>
<td>8.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test

### Table 8.4 – Correlation between gastric emptying rate and antral motility parameters

<table>
<thead>
<tr>
<th>Antral motility parameter</th>
<th>Children with FAP</th>
<th>Healthy controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation</td>
<td>P value</td>
<td>Correlation</td>
</tr>
<tr>
<td></td>
<td>coefficient*</td>
<td></td>
<td>coefficient*</td>
</tr>
<tr>
<td>Fasting antral area</td>
<td>-0.204</td>
<td>0.04</td>
<td>-0.236</td>
</tr>
<tr>
<td>Amplitude of antral contraction</td>
<td>0.322</td>
<td>0.001</td>
<td>0.613</td>
</tr>
<tr>
<td>Frequency of antral contractions</td>
<td>0.292</td>
<td>0.003</td>
<td>0.342</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>0.394</td>
<td>&lt;0.0001</td>
<td>0.597</td>
</tr>
</tbody>
</table>

* Spearman’s correlation coefficient
**Correlation between gastric emptying rate and antral motility parameters**

Table 8.4 demonstrates the relationship between gastric emptying rate and other antral motility parameters. In both patients and controls, gastric emptying rate had a significant correlation with other antral motility parameters.

**DISCUSSION**

This study describes, for the first time, gastric motility in children fulfilling the Rome III criteria for FAP. These children have significantly lower gastric emptying rate, lower frequency and amplitude of antral contractions and antral motility index than healthy controls. Furthermore, they had a significantly wider gastric antrum during fasting period. Gastric emptying rate reveals a negative correlation with the scores obtained for the severity of abdominal pain.

Several studies have reported abnormalities in gastric motility and prolonged gastric emptying among children with FD. Furthermore, adult studies have also reported delayed gastric emptying and antral hypomotility in patients with abdominal pain predominant FGIDs such as FD and IBS. Unlike FD, studies assessing gastric motility in children with FAP were almost non-existing. A previous study has reported significantly prolonged gastric emptying rate and antral motility index in children with non-organic recurrent abdominal pain. In that study, the majority of children recruited had FAP. However, no subgroup analysis was performed to identify the relationship between gastric emptying parameters and the exact type of FGIDs. During the current study we have found delayed gastric emptying, decreased frequency and amplitude of antral contractions and increased fasting antral area, highlighting the gastric motility abnormalities present in children with FAP.

In our study, gastric emptying rate showed a significant negative correlation with the scores obtained for severity of symptoms. The relationship between gastric motility abnormalities and symptoms is not fully understood in patients with functional gastrointestinal disorders. While some adult studies conducted in patients with abdominal pain predominant FGIDs have failed to demonstrate a definite relationship between symptoms severity and motility abnormalities, other studies have shown an association between delayed gastric emptying and bloating, early satiety, postprandial fullness, nausea and vomiting. Lack of relationship between severity of clinical features and motility abnormalities has cast a doubt regarding the pathophysiological association between gastric motility and FGIDs. In this backdrop, the present study has shown a significant correlation between severity of abdominal pain and delayed gastric emptying. This relationship between clinical and physiological parameters suggests the
possibility of delayed gastric emptying playing a role in the pathogenesis of FAP in children. It is possible that delayed gastric emptying associated with poor antral contractions, leads to prolonged gastric stasis and antro-fundic dyscoordination resulting in increased wall tension in the gastric body and the fundus. This in turn may activate tension and pain receptors in the stomach to generate the characteristic periumbilical pain present in children with FAP. Furthermore, heightened visceral sensitivity in these children may also contribute to enhanced pain perception.25,26

Dysfunction at variety of levels of brain-gut axis has been invoked in the pathophysiology of FGIDs. Children with FGIDs are exposed to significantly more stressful events than healthy children.1,2,27 Central dysfunction of brain-gut axis due to emotional stress is suggested as a precipitant of FGIDs and a cause of abnormal gastrointestinal motility.25 Acute and chronic physical stressors, such as labyrinthine stimulation and cold pain have produced a dramatic inhibition of gastric emptying and antral motility.28-30 In contrast to this, a previous study failed to demonstrate a significant difference in gastrointestinal motility in healthy volunteers exposed to psychological stress.31 A pediatric study in children with recurrent abdominal pain also failed to show a significant association between exposure to stressful life events and gastric motility.16 Similarly, we did not find a significant difference in gastric motility parameters and antral motility index between children exposed to stressful life events and those did not expose to such events in the present study.

Motility of the gastric antrum plays a pivotal role in propelling gastric contents into the duodenum through the pylorus. Therefore, poor emptying is expected when there is impaired antral motility. Gastric emptying rate in our patients with FAP showed significant correlation with antral motility parameters. The delayed gastric emptying observed in the majority of our patients with FAP appears to be due to decreased contractile activity of the gastric antrum. Similar finding has been reported in children with recurrent abdominal pain.16 In contrast to this, a previous adult study involving small number (n=15) of healthy volunteers have reported a significant correlation between antral motility and solid emptying, but failed show such definite association with liquid emptying.32 However, in this study, test meal consisted of both liquids and solids, therefore, both liquid and solid emptying were assessed at the same time and the methodology of assessing gastric emptying and antral motility were different. However, in this study, a positive relationship between liquid emptying and antral motility was noted after the end of the initial lag phase for the solids.32 The exact relationship between gastric emptying and antral motility has not been studied in children and adults with FGIDs previously.
Therefore, further studies are needed to clarify the role of abnormal antral motility in functional gastrointestinal diseases in children.

Even though delayed gastric emptying is a common finding in patients with abdominal pain-predominant FGIDs, very few studies have assessed the therapeutic value of gastro-prokinetic drugs in the management. In a previous double-blind placebo controlled trial, domperidone not only improved gastric emptying time and relieved symptoms in patients with functional dyspepsia.10 In contrast to this, several, double-blind placebo-controlled trials on cisapride and mosapride have failed to show significant therapeutic value.33,34 All these therapeutic trials have been conducted in adult patients with functional dyspepsia where the pathophysiology is thought to be multifactorial and the relationship between symptom severity and motility abnormalities are not clear.35 In contrast to this, the correlation between severity of abdominal pain and delayed gastric emptying observed in our study lays a ground to investigate the therapeutic value of gastroprokinetics in the management of children with FAP.

In this study, using a simple, safe and non-invasive ultrasound method, we have shown a significant delay in gastric emptying and impairment in antral motility in children who fulfill Rome III criteria for FAP. Furthermore, we have highlighted the relationship between delayed gastric emptying and severity of abdominal pain. In this light, our findings suggest that delayed gastric emptying and impaired antral motility play a role in the pathogenesis of FAP.

REFERENCES