Digestive Diseases and Sciences, Vol. 36, No. 8 (August 1991), pp. 1066–1073

Abnormalities of Gastrointestinal Motility in Children with Nonulcer Dyspepsia and in Children with Gastroesophageal Reflux Disease

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In 11 children (mean age 44.2 months) with symptoms suggesting upper intestinal dysfunction (nonulcer dyspepsia), in nine children (mean age 27.3 months) with gastroesophageal reflux (GER) disease, and in seven controls (mean age 20.4 months) we investigated fasting [for 3 hr or until two migrating motor complexes (MMC) were observed] and fed (90 min) antroduodenal motility by means of perfused catheter system; furthermore, we measured both gastric emptying of a radiolabeled milk formula and fasting duodenogastric reflux during manometry by assessing bile salt concentration in gastric aspirates. No structural abnormalities of gastrointestinal tract and organic disorders were detected in the patients. In a high proportion of both groups of patients we found manometric abnormalities of interdigestive and fed motor patterns that were not seen in the controls: absence of antral phase III of MMC; significant decrease of antral and/or duodenal motor activity during fasting and/or fed periods; abnormal propagation or configuration of MMC phase III that was significantly shorter than in controls; bursts of sustained fasting and/or fed phasic duodenal activity, frequently uncoordinated with adjacent gut segments. When compared to controls, the mean intragastric concentration of bile salts during all MMC phases and the mean 1-hr percent gastric activity of the radiolabeled milk were significantly higher in the two groups of patients. We conclude that in a high proportion of children with nonulcer dyspepsia and of children with GER disease, gastrointestinal manometry may reveal significant irregularities of antral and duodenal motility, which are associated with increased duodenogastric reflux and delayed gastric emptying.

KEY WORDS: nonulcer dyspepsia; migrating motor complexes; bile salt concentration; gastric emptying.

Nonulcer dyspepsia (NUD) is a clinical entity commonly reported in adults, characterized by intermittent symptoms suggesting dysfunction of upper alimentary tract such as nausea, vomiting, early satiety, and abdominal pain (1–3). Recordings of gastric and small intestinal motor activity give evidence for an association between dyspeptic symptoms and gastrointestinal motility (4–6). Furthermore, scintigraphic or ultrasound studies in dyspeptic patients have shown delayed gastric emptying in many of them (7, 8). Reduced or uncoordi-

Manuscript received March 26, 1990; revised manuscript received October 31, 1990; accepted November 1, 1990.

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0163-2116/91/0800-1066$06.50/0

nated antroduodenal motility has been reported in children with chronic idiopathic pseudoobstruction and in children with recurrent abdominal pain (9, 10). Recently, fasting and fed abnormalities of antroduodenojejunal motility have been reported in children with recurrent functional gastrointestinal symptoms (11). However, gastrointestinal motor activity is rarely investigated in children with symptoms suggesting upper intestinal dysfunction.

Both delayed gastric emptying and antral motor dysfunction also have been found in patients with gastroesophageal reflux (GER) disease (12–14); this would indicate that motor abnormalities in GER disease might extend beyond the lower esophageal sphincter region. However, there are no data on the true prevalence of abnormal gastroduodenal motor activity in a well-defined pediatric population with GER disease.

The present study was designed to investigate the characteristics of fasting and fed antroduodenal motor activity in prospectively selected children with symptoms suggesting upper intestinal tract dysfunction and in children with diagnosed GER disease. We also attempted to define in these groups of patients the relationship between fasting antroduodenal motility and duodenogastric reflux measured simultaneously and between antroduodenal motor patterns and gastric emptying time.

MATERIALS AND METHODS

Subjects. We studied three groups of patients. Eleven children (group I) (mean age ± SD 44.2 ± 37 months; range 4 months to 12 years) had symptoms suggesting dysfunction of upper intestinal tract. None of them had undergone previous abdominal surgery; mechanical obstruction and mucosal diseases were excluded on contrast radiology and upper endoscopy; furthermore, 24-hr intraesophageal pH monitoring did not reveal abnormal GER; finally, infectious, metabolic, and neurologic disorders were also excluded. Chronic unexplained vomiting was present in all patients, associated with epigastric pain (five cases), early satiety (seven cases), anorexia (seven cases), epigastric distension (five cases), failure to gain weight (five cases).

Nine patients (group II) (mean age ± SD 27.3 ± 26 months; range 4 months to 7 years) had protracted GER disease, diagnosed by prolonged intraesophageal pH monitoring, after exclusion of food intolerance, metabolic, and neurologic disorders. In five cases esophagitis was documented by endoscopy and biopsy. Main clinical features were: vomiting and/or regurgitation (eight cases), anorexia (seven cases), wheezing (three cases), nocturnal cough (two cases), failure to gain weight (five cases), epigastric distension associated with vomiting (three cases).

Seven children (group III) (mean age ± SD 20.4 ± 14.4 months; range 6 months to 12 years) served as controls: four were affected by functional constipation; one had milk intolerance; two were affected by chronic nonspecific diarrhea. Parents gave informed consent and the study protocol was approved by the ethical committee of our faculty.

Gastrointestinal Manometric Technique. Gastrointestinal manometry was performed after an overnight fast with a four-lumen tube (OD 3.6 mm) introduced transnasally along a guidewire. Each catheter was perfused with distilled water via a pneumohydraulic pump (Arndorfer Medical Specialties) at a rate of 0.3 ml/min and attached to strain gauge transducers (Statham P23D), the output of which was recorded on a polygraph (Beckman R611). The probe was positioned under fluoroscopy, so that two proximal recording sites (spaced 0.5 cm apart) were located in the distal antrum and the other two openings in the descending duodenum and at level of Treitz's angle, respectively. Two probes with different distributions of intestinal side openings were used: the first consisted of intestinal ports 5 cm apart, the proximal of which was 7 cm beyond the distal antral opening and was used in children less than 6 years old; in the other probe the two intestinal ports were 8 cm apart, with the proximal 8 cm beyond the distal antral side opening and was used in children older than 6 years. The manometric probe was positioned under fluoroscopy that was available during all the recording sessions in order to check for correct positioning across the antroduodenal region. A polyvinyl probe then was introduced through the nose and positioned with its tip in the most dependent portion of the stomach for continuous aspiration of gastric content.

Fasting motility was recorded for 3 hr or until two migrating motor complexes (MMCs) were observed and for 90 min after administration of a 300-kcal homogenized meal consisting of 25% protein, 20% fat, 55% carbohydrate (rice flour, oil, meat powered). After ingestion of the meal, position of the probe across the gastroduodenal junction was fluoroscopically checked and eventually corrected because of postcibal accommodation of the stomach.

Gastrointestinal motility was assessed qualitatively and quantitatively. Three phases of fasting antroduodenal motor activity were identified (Figure 1): phase I, characterized by almost complete motor quiescence; phase II, consisting of spontaneous irregular activity followed by an uninterrupted short burst of phasic activity migrating abnormally (phase III or activity front). The following motility variables were calculated: (1) duration of the cycles, ie, the time interval between the end of one duodenal activity front and the end of the next; (2) duration of each phase of the interdigestive cycle, calculated as mean value if each MMC phase was observed more than once; (3) motility index (MI) of antral activity, calculated during phase II as sum of amplitude (mm Hg) multiplied by the number of contractions for each 5-min period and expressed as mean of the various 5-min values; a final mean value was calculated for the two antral recording sites. Antral MI also was measured for fed motility and calculated as during fasting analysis. Normal values for gastrointestinal motor variables have

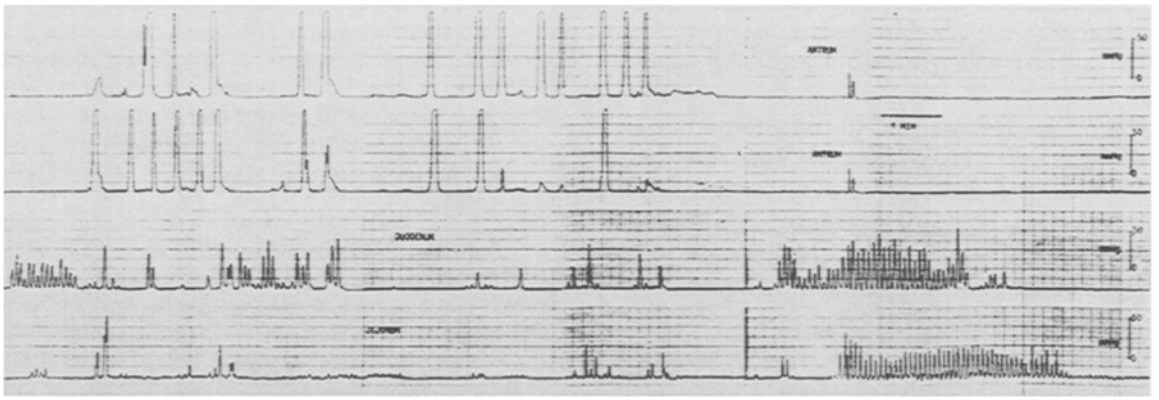

Fig 1. Regular occurrence of migrating motor complex at the level of the antrum (first two channels), of the duodenum (third channel), and of the jejunum (fourth channel). Phase III, characterized by an uninterrupted burst of phasic contractions, propagates from the antrum to the jejunum; it is preceded by an irregular phasic activity (phase II) and followed by phase I, a period of motor quiescence.

been defined previously in term infants, children, and adolescents (10, 15–17).

Gastric aspirates were collected during the fasting recording period and pooled in 10-min samples for determination of bile salt concentration to give an index of duodenogastric reflux. Gastric aspirates were collected into glass tubes and stored at −20° C for subsequent analysis. Total bile acid concentration was determined by steroid dehydrogenase method (18). All determinations of "specific activity" were made in duplicate, the mean coefficient of variation being 5%.

Gastric emptying was measured by radioscintigraphy. Patients fasted 6–8 hr before ingestion of cow's milk labeled with technetium-99m sulfur colloid (100 μCi), in a volume similar to that usually taken at breakfast. Within 5 min after beginning the meal, children were positioned supine under a gamma camera. Gamma emissions were counted for 60 intervals of 1 min, while subjects remained as quiet as possible during the study. Scan data were stored in an on-line computer for subsequent analysis. Gastric emptying was expressed as percentage, $[(CT_0 - CT_t)/CT_0] \times 100$, where CT_0 is the initial count rate of isotope in the stomach, and CT_t is count rate of ^{99m}Tc at any time in the stomach after correction for isotope decay.

Statistical Analysis. The statistical analysis was performed using the appropriate tests (Student's t test, Wilcoxon rank-sum test) with $P < 0.05$ being considered significant. Results are given as mean ± SD.

RESULTS

In all controls, regular occurrence of interdigestive motility cycles was recognized, with phase III activity starting in the antrum and propagating distally (Figure 1). The duration of phase III, calculated from the duodenal port was 4.42 ± 1.26 min; length of interdigestive cycles was 55.3 ± 11.6 min, 22.07% of which was occupied by phase I, 69.9% by phase II, and 8.03% by phase III activity. Phase III of MMC was undetected in the antrum in 12 patients (seven of group I and five of group II) (Figure 2). Length of the interdigestive cycle (minutes) in the patients did not differ from that of controls (group I: 57.9 ± 23.01; group II: 75.6 ± 27.02), but duodenal phase III was significantly shorter (minutes) than in controls (group I: 3.03 ± 0.75; group II: 3.24 ± 1.22; $P < 0.05$) (Figure 3). Both fasting and fed antral motility indexes (×10) were significantly reduced in the two groups of patients (fasting: group I, 256.09 ± 225; group II, 368 ± 239), (fed: group I, 208.09 ± 106.16; group II, 466 ± 337) as compared to controls (fasting: 832 ± 192.4, $P < 0.05$); fed 1104 ± 298, $P < 0.05$). Fasting and/or fed antral hypomotility was often associated with duodenal and jejunal hypomotility (Figures 4–6); these manometric findings were frequently coincident with dyspeptic symptoms such as nausea, epigastric fullness, pain, and vomiting. In a high proportion of the patients, we found abnormal manometric patterns that were not seen in the controls: abnormal propagation or configuration of the activity front was evident in six patients of group I and in two patients with GER disease. Bursts of sustained fasting and/or fed phasic duodenal activity were observed in seven patients of group I and in five patients of group II; these bursts were usually not propagated or uncoordinated with adjacent intestinal segments (Figure 7). The mean concentration of bile salts was significantly higher in both groups of patients than in controls during all the phases of the MMC (Tables 1 and 2); furthermore, after occurrence of phase III, bile salt concentration significantly decreased in controls, but remained statistically unchanged in both groups of patients. Percent gastric isotope activity at 60 min

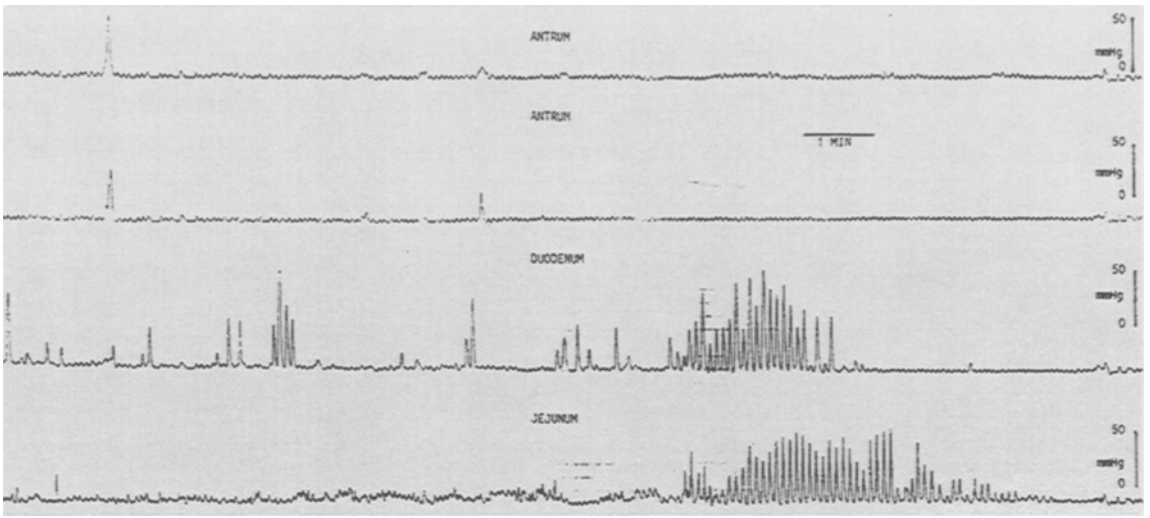

Fig 2. Absence of phase III of the MMC in the antrum.

was significantly higher in the patients than in controls (controls: 38.1 ± 6.5; group I: 62.18 ± 14.17, $P < 0.05$; group II: 64.22 ± 15.03, $P < 0.05$). Highest degrees of both intragastric bile salt concentration and 1-hr gastric isotope retention were detected in patients with the most marked motor irregularities (Tables 1 and 2).

DISCUSSION

In this study we have provided direct evidence of abnormal gastrointestinal motility in children investigated for recurrent symptoms suggesting upper intestinal dysfunction and in children with protracted GER disease. We identified various patterns of abnormal gastrointestinal motility that can be summarized as follows: absence of antral phase III of MMC; reduced antral and/or duodenojejunal motility during fasting and/or fed periods; diminished length of MMC phase III, which was sometimes irregularly propagated; irregular bursts of small intestine motility frequently not propagated and/or uncoordinated with adjacent segments. These irregular patterns can be responsible for disturbances of gastrointestinal motor functions. Indeed, the majority of our patients have delayed emptying of a liquid meal. In past years it has been generally agreed that liquids are primarily emptied by a driving force due to sustained pressure exerted by the proximal stomach (19); however, it also has been reported that antral peristalsis can contribute

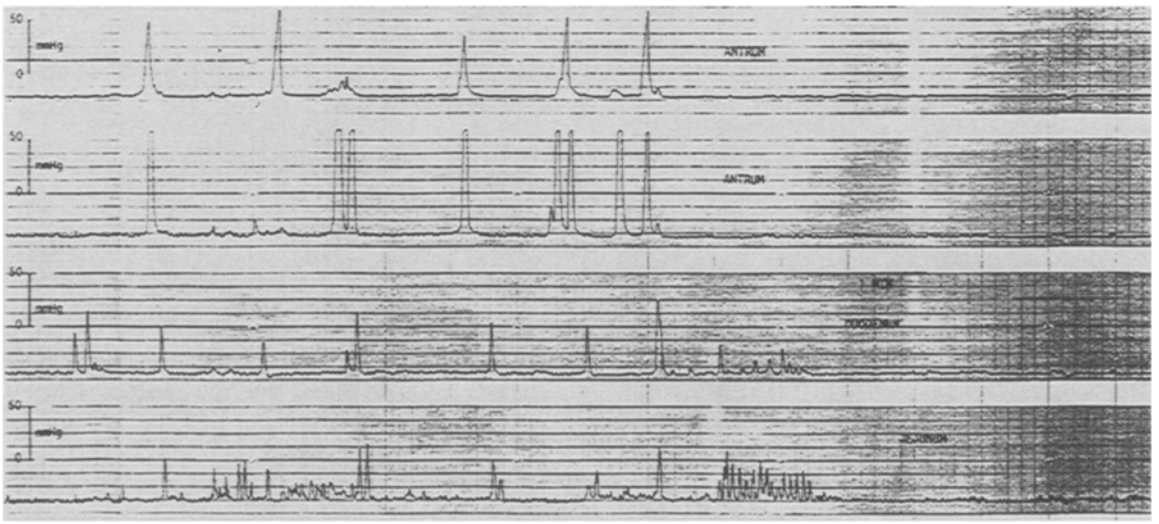

Fig 3. Phase III is absent at the level of the duodenum and appears to be short-lasting in the jejunum.

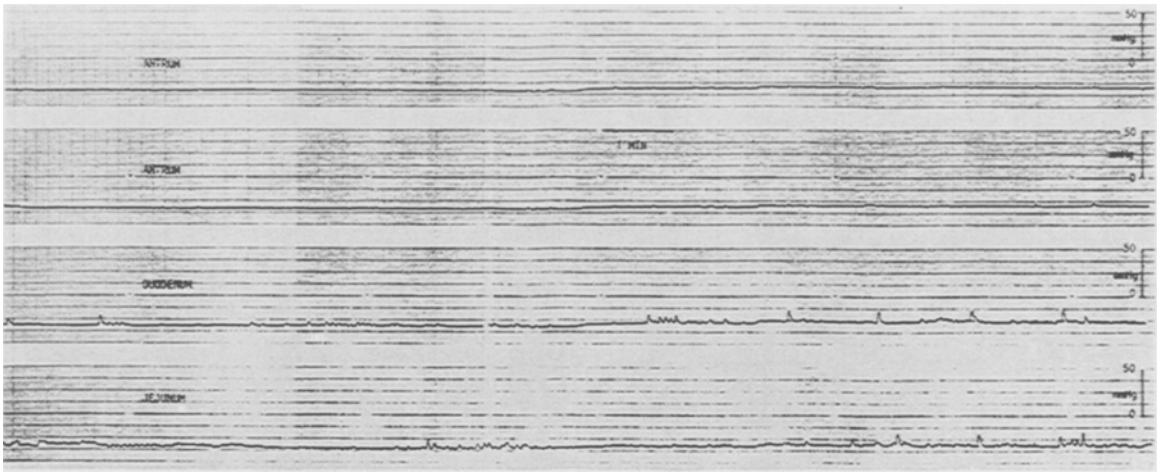

Fig 4. Severe antroduodenojejunal hypomotility recorded during fasting period.

to propulsion of liquids into the small intestine (20). Furthermore, irregular or segmenting duodenal contractions, such as those described in some of the patients, might counteract the gastric driving action by braking gastric outflow (21–23). On the other hand, we cannot exclude that other regions of the stomach (ie, fundus) were affected simultaneously. Finally, alteration of fasting antroduodenal motility

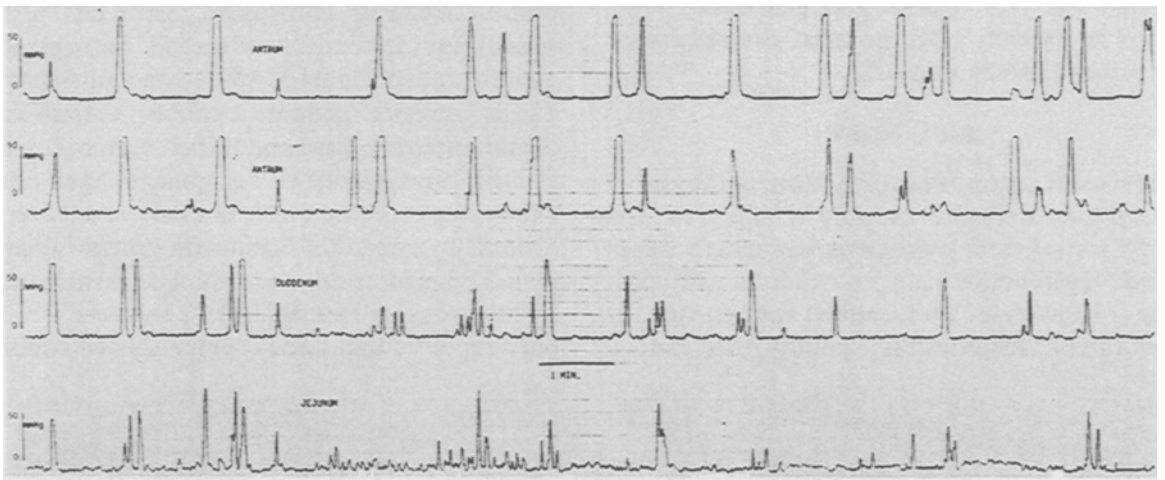

Fig 5. Regular postprandial motor pattern at level of antrum, duodenum, and jejunum.

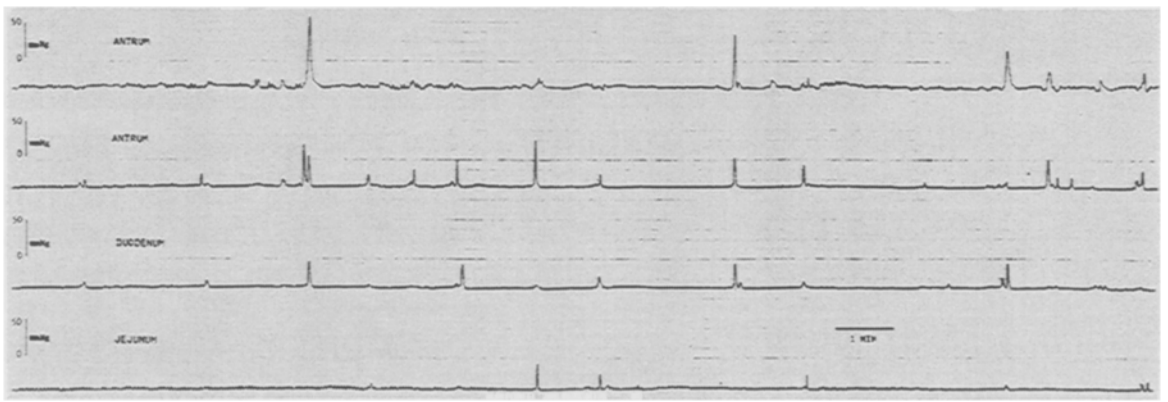

Fig 6. Marked antroduodenojejunal hypomotility recorded during fed period.

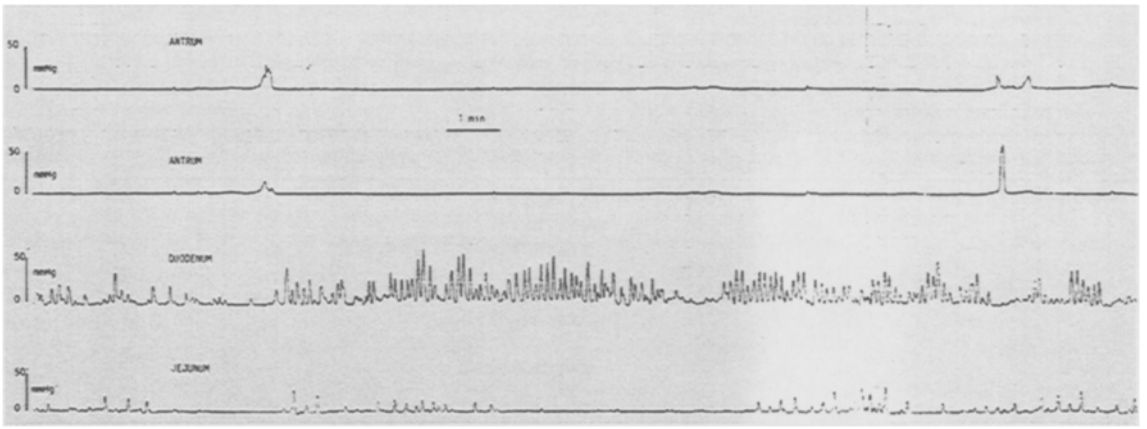

Fig 7. Fasting recording of antroduodenojejunal motility showing antral hypomotility and bursts of continuous phasic motor activity at the level of the duodenum; the latter appears to be uncoordinated with the distal intestinal segment.

(particularly short duration or abnormal propagation and configuration of MMC phase III) also might contribute to gastric stasis, as it is believed that activity fronts are implicated in the gastric outflow during the late postprandial period (24).

It is still an unsettled matter how gastrointestinal motor irregularities, such as those detected in our patients, can be responsible for dyspeptic symptoms. They could determine gastric stasis or increase duodenogastric reflux; these events frequently are reported in adults with nonulcer dyspepsia (25, 26). Furthermore, motor abnormalities could conceivably be responsible for symptoms via spasm or distension of intestinal wall. However, if disordered motility is believed to be the cause of symptoms, a temporal relationship over time between motility and symptoms must be reported. Recently, an association between irregular jejunal motility and abdominal pain in adults with irritable bowel syndrome and between motion sickness and gastric dysrhythmias has been reported (27, 28); data on the temporal relationship between symptoms and abnormal patterns of gut motility remain scanty. Probably, development of portable devices for long-term manometric measurement might help for this purpose.

The presence of abnormalities of fasting and/or fed antroduodenal motility in children with GER disease is of great interest. Previous studies have shown that patients with GER disease may exhibit antral hypomotility and delayed gastric emptying of solid and liquid meals (12–14). Our results suggest that motor dysfunction in reflux disease can extend beyond the gastroesophageal junction and involve the stomach and duodenum as well. We would

TABLE 1. GASTROINTESTINAL MOTILITY PATTERNS, INTRAGASTRIC CONCENTRATION OF BILE ACID (BA) AND GASTRIC EMPTYING IN CHILDREN WITH RECURRENT VOMITING AND DYSPEPTIC SYMPTOMS

	*BA concentration (mg/ml)**			*Gastric emptying*	*Antral*	*Duodenojejunal*	*Abnormal duodenojejunal*	*Duodenojejunal*
Cases	*Phase I*	*Phase II*	*Phase III*	*(% of activity)†*	*hypomotility*	*hypomotility*	*phase III*	*dysmotility*
F.G.	1.24	1.98	0.74	83	fasting, fed			yes
M.G.	0.88	1.4	1.3	65	no phase III	fasting, fed	yes	
F.M.	0.22	0.21	0.22	74	fed no phase III			
D.R.	0.21	0.43	0.37	45	no phase III			
R.P.	0.65	1.1	0.86	64	fasting, fed no phase III		yes	yes
P.A.	0.45	0.51	0.39	78	fasting			yes
C.F.	1.0	3.3	2.03	69	no phase III	fed	yes	yes
D.A.	0.85	1.38	1.30	44	fasting, fed		yes	yes
B.N.	0.12	0.17	0.15	48	no phase III			
R.A.	0.65	0.61	0.78	42			yes	yes
P.T.	0.48	0.70	0.68	72	fasting, fed no phase III		yes	yes

*Mean (±SD) values—phase I: 0.61 ± 0.34, phase II: 1.07 ± 0.88; phase III: 0.8 ± 0.53. Intragastric bile acid concentration in controls [mean (±SD) and range]—phase I: 0.15 ± 0.14 (0.04–0.43); phase II: 0.32 ± 0.30 (0.14–1.03); phase III: 0.11 ± 0.09 (0.03–0.38).
†Mean (±SD) value: 62.18 ± 14.17.

TABLE 2. GASTROINTESTINAL MOTILITY PATTERNS, INTRAGASTRIC CONCENTRATION OF BILE ACID (BA) AND GASTRIC EMPTYING IN CHILDREN WITH GASTROESOPHAGEAL REFLUX DISEASE

Cases	BA concentration (mg/ml)*			Gastric emptying (% of activity)†	Antral hypomotility	Duodenojejunal hypomotility	Abnormal duodenojejunal phase III	Duodenojejunal dysmotility
	Phase I	Phase II	Phase III					
D.P.	0.45	1.66	1.61	68	fasting, fed no phase III			yes
M.M.	1.24	1.4	1.98	84	no phase III	fasting, fed		
C.M.	0.03	0.06	0.04	58			yes	yes
D.A.	0.45	1.79	1.7	74	fast, fed no phase III			yes
M.A.	0.75	0.71	0.15	41				
F.S.	0.49	0.52	0.47	68	no phase III		yes	yes
S.M.	0.07	0.08	0.03	37				
D.C.	0.57	0.47	0.42	72		fasting, fed		
C.P.	0.45	0.39	0.51	76	no phase III			yes

*Mean (±SD) values—phase I: 0.50 ± 0.33; phase II: 0.78 ± 0.62; phase III: 0.76 ± 0.72. Intragastric bile acid concentration in controls [mean (±SD) and range]—phase I: 0.15 ± 0.14 (0.04–0.43); phase II: 0.32 ± 0.30 (0.14–1.03); phase III: 0.11 ± 0.09 (0.03–0.38).
†Mean (±SD) value: 64.22 ± 15.03.

propose that some cases of GER disease represent a primary motor disorder of gastroduodenal tract: uncoordinated or decreased antroduodenal motility, indeed, can delay gastric emptying and lead to gastric distension. Once this has occurred, the lower esophageal sphincter (LES) might undergo phasic transient relaxation with consequent reflux of gastric content into the esophagus. Experimental observations in man have suggested that gastric distension is responsible for the increased rate of transient LES relaxation, which is the most common mechanism of GER in subjects with GER disease (29).

Both groups of patients had higher intragastric levels of bile salts during all the phases of interdigestive activity. Presence of bile salts in the stomach is a regular event during fasting and after eating, more reflux being usually observed during phase II of the migrating complex, while activity fronts and coordinate antroduodenal activity are able to lower gastric bile salt concentration (30, 31).

Either decreased antral pressure or disordered duodenal motility seem to be implicated in increasing bile reflux into the stomach (32, 33). Therefore, it is not surprising that higher intragastric levels of bile salts were detected in our patients in comparison with controls during all the MMC phases, particularly after occurrence of activity fronts that were frequently absent in the stomach or irregularly propagated or short lasting.

The etiology of motor irregularities described in this study is unknown. Most manometric patterns found in our patients suggest neurologic or myogenic alterations and also are reported in patients which chronic intestinal pseudoobstruction (34, 35). However, even if pathological studies of neurogenic or myogenic intestinal structures were not performed, intestinal pseudoobstruction in our patients was unlikely. Indeed, radiology did not show dilatations or spasms in any of the patients; furthermore, no evidence of extraintestinal myogenic or neurogenic dysfunction was reported, and none of the patients showed clinical deterioration or occlusive episodes at prolonged follow-up (36). Whether functional nonulcer dyspepsia and chronic idiopathic intestinal pseudoobstruction are part of the spectrum of the same disease remains to be determined.

We conclude that children with functional dyspepsia and children with GER disease may exhibit significant abnormalities of gastric and duodenal motility during fasting and/or fed periods. These abnormalities seem to be associated with impaired gastric emptying and increased degrees of duodenogastric reflux. Gastrointestinal manometry is a feasible and useful diagnostic technique in the clinical investigation of children with symptoms suggesting altered upper gut function; it also may provide a basis for development of a rational therapeutic approach with drugs acting on gastric and intestinal motility. Further studies, however, should be undertaken in order to better understand the relationship between dyspeptic symptoms and intestinal motor function.

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