

Vomiting and Gastric Motility in Infants With Cow's Milk Allergy

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ABSTRACT

Background: Regurgitation and vomiting are common manifestations of cow's milk protein allergy (CMPA) in infants and are usually ascribed to gastroesophageal reflux (GER). Gastric anaphylaxis can induce antral dysmotility in the rat, and therefore the hypothesis for the current study was that cow's milk in sensitized infants may impair antral motility, thereby promoting GER and reflex vomiting.

Methods: Seven vomiting infants with CMPA and nine with primary GER underwent a challenge with cow's milk formula. Electrogastrography (EGG) was used to measure the spectral frequency (bradygastria = 1.5–2.4 cycles per minute [cpm], normogastria = 2.5–3.9 cpm, tachygastria = 4.0–9.0 cpm) and the postprandial-to-fasting power ratio of gastric electrical activity, whereas gastric half-emptying time ($T_{1/2}$) was measured by electrical impedance tomography (EIT).

Results: In CMPA and GER, respectively, during fasting, the frequency distribution (mean \pm SD) of the EGG was as follows: normogastria 47.9% \pm 12.5% versus 52.2% \pm 9.8%, bradygastria 24.1% \pm 5.7% versus 22.8% \pm 8.3%, and tachygastria

28.0% \pm 8.5% versus 25.0% \pm 8.3%. In contrast, after the cow's milk challenge, the difference between the two groups was statistically significant: normogastria 33.1% \pm 8.8% versus 70.6% \pm 8.6% ($P < 0.0001$), bradygastria 38.0% \pm 15.5% versus 15.7% \pm 5.2% ($P = 0.002$), and tachygastria 28.9% \pm 10.6% versus 13.4% \pm 4.6% ($P = 0.001$). The postprandial/fasting power ratio (mean \pm SD) was 3.2 \pm 1.9 in CMPA and 8.1 \pm 2.1 in GER ($P < 0.0001$). Gastric $T_{1/2}$ (mean \pm SD) of the cow's milk meal was 89.0 \pm 26.3 minutes versus 54.0 \pm 12.6 minutes ($P = 0.003$). In infants with GER all EGG parameters and gastric $T_{1/2}$ were similar to that in 10 healthy control infants.

Conclusions: In sensitized infants, cow's milk induces severe gastric dysrhythmia and delayed gastric emptying, which in turn may exacerbate GER and induce reflex vomiting. Electrogastrography and EIT can be useful in the assessment of vomiting, GER, and CMPA in infants. *JPGN* 32:59–64, 2001.

Key words: Cow's milk protein allergy—Electrical impedance tomography—Electrogastrography—Gastroesophageal reflux—Vomiting. © 2001 Lippincott Williams & Wilkins, Inc.

Adverse reactions to food are most prevalent in the first 2 years of life, affecting approximately 8% of infants (1). Food hypersensitivity, or allergy (adverse reactions due to immunologic mechanisms), accounts for most of these reactions. Cow's milk alone, with its antigen protein fractions lactalbumin, β -lactoglobulin, and casein appears to be the most common culprit, producing adverse reactions in approximately 2.5% of young infants (2).

The skin and the gastrointestinal tract are the most common target organ of food hypersensitivity reactions in young infants, in whom respiratory manifestations and severe anaphylaxis with shock are fortunately uncommon. Regurgitation and vomiting are frequent gastroin-

testinal manifestations of immunoglobulin (Ig)E-mediated cow's milk protein allergy (CMPA) in young infants. Often, however, a misdiagnosis of primary gastroesophageal reflux (GER) disease is made, which may also be reinforced by the findings of an eosinophilic infiltrate of the lower esophageal mucosa at endoscopy (3) and an abnormal acid exposure in intraesophageal 24-hour pH study (4).

In egg albumin-sensitized rats, intragastric antigen challenge leads to delayed gastric emptying, which is associated with a transient reduction in gastric antral contractions (5). Gastric luminal antigen challenge results in IgE-mediated mucosal mast cell degranulation and the release of a variety of substances including histamine, 5-hydroxytryptamine (5-HT), prostaglandins, leukotrienes, and platelet activating factor (PAF), all of which can influence gastrointestinal motility. Thus, we hypothesized that cow's milk challenge in sensitized infants may impair gastric antral motor activity and gastric emptying, thereby promoting GER and reflex vomiting.

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PATIENT POPULATION

Patients

We studied 7 infants (Table 1) aged 1 to 7 months (median, 6.5) with recurrent regurgitation and vomiting as the most prominent symptom related to CMPA, which had been diagnosed 2 to 12 weeks (mean, 5) before on the basis of a prompt clinical remission after beginning a cow's milk-free diet with or without a positive skin prick test or radioallergosorbent test (RAST) and a positive response to a cow's milk challenge. All infants were consuming a balanced cow's milk-free diet, including soy-based, casein hydrolysate, or whey hydrolysate formula, and the mother of a breast-fed child was consuming a cow's milk-free diet, at the time of investigation. Three of the infants had already been weaned. Symptoms other than regurgitation and vomiting (excessive crying and/or colicky abdominal pain, eczema, diarrhea) had also promptly subsided with institution of the cow's milk-free diet. In one infant, allergic reactions had eventually developed to soy (eczema, vomiting, and diarrhea). All the infants had a positive family history of atopy (at least one first-degree relative affected by allergic reactions of some sort).

Control Subjects

We also studied nine infants (Table 1) aged 2 to 16 months (median, 4.5) with recurrent regurgitation and vomiting due to primary uncomplicated GER diagnosed 4 to 10 weeks (mean, 7) earlier on the basis of a positive response to conservative antireflux treatment (i.e., postural therapy and thickened food) plus cisapride (0.2 mg/kg four times daily) in four of nine infants. Some of these infants also had other symptoms, such as excessive crying and arching of the back at meals, which also subsided with treatment. The absence of major complications related to reflux (i.e., failure to thrive, hematemesis, or respiratory problems) together with the prompt response to conservative and medical treatment and the presence of typical reflux symptoms (regurgitation and vomiting) did not indicate the need for invasive investigations such as endoscopy and intraesophageal pH monitoring. All these infants were consuming an otherwise normal diet (including cow's milk and dairy products) for their age, and five of them had been weaned. In the four infants who were taking cisapride, the drug was discontinued 72 hours before the tests.

Ten age-matched healthy infants without any gastrointestinal symptoms who had been previously tested during validation of our noninvasive gastric motility tests were taken from our database and acted as healthy control subjects (Table 1).

Depending on their ages, the subjects were tested with either cow's milk or cow's milk-based starting or follow-up formula (20 mL/kg body weight up to a maxi-

TABLE 1. Demographic and clinical features of patients and controls

Group	No. subjects	Median age in months (range) at investigation	Median age in months (range) at onset	Clinical symptoms	+VE family history for atopy	Skin prick or RAST +VE to cow's milk	Biochemistry (FBC, RFT, LFT, metabolic*, urine†)	Treatment
Cow's milk allergy	7	6.5 (1.0–7.0)	1.25 (0.5–2.0)	Vomiting (7/7) Excessive crying (7/7) Eczema (3/7) Diarrhea (2/7)	7/7	4/6	Normal	Cow's milk-free diet
Gastroesophageal reflux (GER)	9	4.5 (2.0–16.0)	1.0 (0.5–1.25)	Vomiting (9/9) Excessive crying (5) "Arching" at meals (5)	2/9	0/2	Normal	Posture (9) Thickened feeds (9)
Healthy infants	10	6.0 (2.0–12.0)	—	None	1/10	ND	ND	Cisapride (4) None

FBC, full blood count; RFT, renal function tests; LFT, liver function tests; ND, not determined.

* Metabolic = blood ammonia, pyruvate, lactate, blood gas.

† Urine = urinalysis, culture.

Clinical symptoms: number of patients with clinical symptoms/number of patients in group.

+VE family history for atopy: number of patients with positive family history/number of patients in group.

Skin prick or RAST +VE to cow's milk: number of patients who tested positive/number of tested patients in group.

Treatment: number of treated children/number of patients in group.

mum of 250 mL), with 0.22 g/100 mL NaCl added to increase electrical conductivity, as previously described (see later discussion).

Written informed consent to perform the tests had been obtained from all parents of patients and control infants.

METHODS

Electrogastrography (EGG)

Surface EGG (6) (Synectics Medical Ltd., Stockholm, Sweden) was used to detect gastric antral electrical activity over a 2-hour fasting and postprandial period. After detersion and gentle abrasion of the skin to reduce impedance (mean \pm SD impedance: 2.5 ± 2.0 k Ω , two Ag/AgCl electrodes were attached to the abdominal skin overlaying the gastric antrum. The electrical signal was amplified and low-pass filtered at 0.33 Hz, digitalized at 1 Hz by an inbuilt analogue-to-digital converter, and stored on a portable Digitrapper (Synectics) for off-line analysis. The digitalized EGG signal was then subjected to running spectral analysis using a series of modular computerized algorithms (PC-Dats; Prosig Computer Consultants, Fareham, UK), as previously described (7). Autoregressive modeling (8) was used to detect the power spectra in cycles per minute (cpm), their distribution within three major frequency bands—1.5 to 2.4 cpm (bradygastria), 2.5 to 3.9 cpm (normogastria) and 4.0 to 9.0 cpm (tachygastria)—and the power of the EGG signal during the fasting and postprandial period, from which the postprandial-to-fasting power ratio was calculated. The resultant analysis was displayed as a pseudo three-dimensional plot.

Electrical Impedance Tomography

Gastric emptying of the test meal was simultaneously measured by EIT using an ambulatory applied potential tomography system (Institute of Bioelectrical Engineering and Services, University of Sheffield, Sheffield, UK) (9). An alternating current of 5 mA at 50 kHz peak to peak, produced by a dedicated portable unit was passed between each pair of 16 electrodes placed circumferentially around the abdomen, and the potential differences between all the remaining electrode pairs were measured during each cycle, which lasted 80 msec. Three hundred cycles were added together to form a data set, or frame. A reference frame was collected just before the meal, and the frames collected during and after the meal were back projected against it to produce, through an image reconstruction algorithm, sequential cross-sectional images related to changes in intragastric resistivity. Time to half-emptying ($T_{1/2}$) was calculated as the time required to achieve a 50% decrease of the maximum conductivity recorded in the stomach area at the end of the meal. With this technique, GER episodes occurring during or after a milk meal can also be detected as sudden peaks of reduced intragastric resistivity (10).

Statistical Analysis

A *t*-test for paired data was used to compare fasted EGG with postchallenge EGG frequencies in patients with CMPA, pa-

tients with GER and healthy control infants, whereas a *t*-test for unpaired data was used to compare postchallenge EGG frequencies as well as postprandial-to-fasting power ratio of the EGG between patients with CMPA, patients with GER, and healthy control infants. The Mann-Whitney test was used to compare gastric emptying $T_{1/2}$ in infants with CMPA and infants with GER with healthy control subjects. Ninety-five percent confidence intervals (95% CIs) for the difference between means were calculated, and the differences were considered to be statistically significant whenever $P < 0.05$.

RESULTS

Gastric Antral Electrical Activity

During the fasting state, the frequency distribution (mean \pm SD) of the EGG was similar in infants with CMPA, control infants with primary GER, and healthy control infants: normogastria 47.9% \pm 12.5% versus 52.2% \pm 9.8% and 50.3% \pm 9.4%, bradygastria 24.1% \pm 5.7% versus 22.8% \pm 8.3% and 28.7% \pm 10.6%, and tachygastria 28.0% \pm 8.5% versus 25.0% \pm 8.3% and 21.0% \pm 7.9%, respectively. In contrast, after the cow's milk meal the frequency distribution of the EGG was as follows: normogastria 33.1% \pm 8.8% versus 70.6% \pm 8.6% (95% CI, -46.8 to -28.0, $P < 0.0001$), bradygastria 38.0% \pm 15.5% versus 15.7% \pm 5.2% (95% CI, 9.6-33.9, $P = 0.002$), and tachygastria 28.9% \pm 10.6% versus 13.4% \pm 4.6% (95% CI, 7.2-24.1, $P = 0.001$) in allergic infants and infants with primary GER, respectively (Fig. 1). In healthy control infants, the frequency distribution of the postprandial EGG (normogastria 69.6% \pm 7.8%, bradygastria 18.5% \pm 4.7%, and tachygastria 11.9% \pm 7.5%) was similar to that of infants with GER and therefore significantly different from that of infants with CMPA (Fig. 1). The postprandial-to-fasting power ratio (mean \pm SD) was 3.2 \pm 1.9 in infants with CMPA, 8.1 \pm 2.1 in infants with GER (95% CI, -7.1 to -2.7, $P < 0.0001$) and 7.1 \pm 2.4 in healthy control infants. Unlike healthy infants and infants with primary GER, in whom, as expected, the EGG power increased after the meal, in several patients with CMPA, the power of the EGG sig-

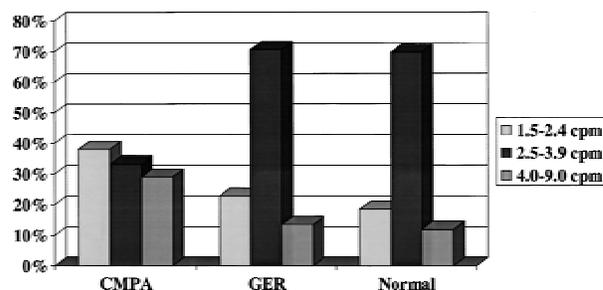


FIG. 1. Frequency distribution of the postchallenge electrogastrogram in infants with regurgitation and vomiting due to cow's milk protein allergy, infants with primary gastroesophageal reflux, and control healthy infants.

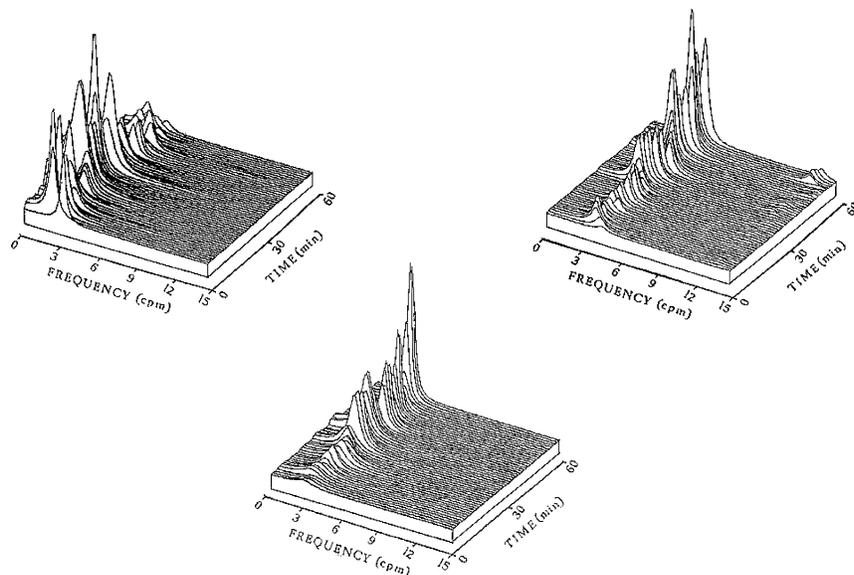


FIG. 2. Pseudo three-dimensional running spectral frequency time, amplitude plots of three electrogastragrams from (A) an infant with regurgitation and vomiting due to cow's milk allergy, (B) an infant with regurgitation and vomiting due to primary gastroesophageal reflux, and (C) a control healthy infant. The cow's milk meal was given at 30 minutes. In (A) the electrogastragram power markedly decreases, and the frequency becomes unstable after the cow's milk meal, whereas in (B) and (C) normal 3-cpm activity is clearly seen throughout the recording, and the EGG power increases after the test meal.

nal significantly decreased after the cow's milk challenge (Fig. 2). Therefore, after the cow's milk challenge, allergic infants showed a significant decrease or a suppression of 2.5 to 3.9 cpm activity (95% CI, 3.7–25.7, $P = 0.017$) matched by an increase of bradygastria (95% CI, –26.4 to –1.34, $P = 0.035$), whereas infants with primary GER showed an increase of 2.5 to 3.9 cpm activity (95% CI, –27.5 to –9.2, $P = 0.002$) related to a decrease of both bradygastria and tachygastria, similar to healthy control infants.

Gastric Emptying

Gastric $T_{1/2}$ (mean \pm SD) of the cow's milk formula meal was 89.0 ± 26.3 minutes (range, 63–140) in infants with CMPA and 54.0 ± 12.6 minutes (range, 34–73) in infants with GER (95% CI, 12.0–55.0, $P = 0.003$) and 62.4 ± 13.3 (range, 38–80) in healthy infants. Gastric emptying in infants with primary GER was therefore similar to that of healthy infants. The EIT gastric emptying profiles showed evidence of GER episodes (Fig. 3) in six patients (four of seven with CMPA and two of nine with primary GER), all of whom vomited mouthfuls of formula during the test, thereby reducing the meal volume.

Clinical Symptoms

Either during the challenge and/or within the following 24 hours, all seven patients with CMPA, versus six of nine control infants with primary GER, had recurrent episodes of regurgitation and/or vomiting. Furthermore, among the infants with CMPA, five had colicky abdominal pain, and two had diarrhea.

DISCUSSION

Our data clearly show that in infants sensitive to cow's milk protein, a challenge with cow's milk results in a significant impairment of gastric motor function. More specifically, in infants with GER secondary to CMPA, but not in infants with regurgitation and vomiting related to primary GER, a cow's milk challenge induces gastric dysrhythmia. Such gastric dysrhythmia consists of unstable electrical activity for which no dominant frequency can be identified, resulting from decreased normogastria and increased bradygastria activity, and a significantly smaller increase of the postprandial-to-fasting power ratio. Furthermore, gastric emptying of a standard cow's milk formula meal is significantly delayed in in-

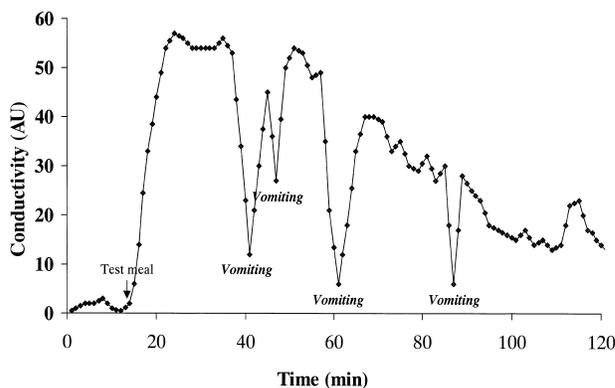


FIG. 3. Electrical impedance tomography gastric emptying profile in an infant with cow's milk protein allergy who vomited mouthfuls repeatedly during the challenge with a cow's milk formula meal. Vomiting episodes appear as sharp peaks of decreased conductivity (subtraction of meal from the stomach). In spite of vomiting, gastric emptying in this infant was delayed (90 minutes).

fants with GER secondary to CMPA, compared with infants with primary GER. The degree of gastric motor dysfunction induced by a cow's milk meal in infants with CMPA is further emphasized by the fact that gastric emptying was significantly delayed in this group of patients, even if they all vomited during the test, thereby reducing the intragastric volume.

Delayed gastric emptying results in prolonged gastric distension. Gastric (especially antral) distension in turn stimulates mechanoreceptors and activates the afferent (vagal) limb of the emetic reflex. After activation of the emetic reflex, the gastric fundus relaxes, the gastric pacemaker is inhibited, and antroduodenal dysrhythmias occur, leading to impaired gastroduodenal motility and gastroparesis (11). Delayed gastric emptying and gastric (especially fundus) distension, either related to a primary disorder of gastric motility or secondary to activation of the emetic reflex, can themselves induce transient and inappropriate relaxations of the lower esophageal sphincter, which are the most important pathogenetic factors in GER. Indeed, the rate of gastric emptying often correlates with the severity of GER (12) and the presence of esophagitis (13). Therefore, in infants sensitive to cow's milk, vomiting most likely results from GER as well as the emetic reflex, with the former being worsened and the latter being triggered by the gastric dysmotility and delayed gastric emptying induced by a cow's milk challenge.

In infants with CMPA, gastric dysrhythmia and delayed gastric emptying are usually associated with or followed by symptoms such as regurgitation, vomiting, colicky abdominal pain, and diarrhea. Gastric dysrhythmia and delayed gastric emptying have been demonstrated in a variety of pediatric disorders characterized by recurrent nausea and vomiting, in which all the different control levels of gastrointestinal motility, smooth muscle (7), enteric nervous system (7), extrinsic innervation (14), and polypeptide hormones (15) may be affected. In infants with CMPA, at least the enteric neuromusculature is disturbed, with gastric antral dysrhythmias possibly resulting from abnormal activation and stimulation of smooth muscle cells by polypeptides and proinflammatory cytokines. In egg albumin-sensitized rats, intragastric antigen challenge leads to delayed gastric emptying, which is associated with a transient reduction in gastric antral contractions (5,16). Gastric luminal antigen challenge results in IgE-mediated mucosal mast cell degranulation and the release of a variety of substances including histamine, 5-HT, prostaglandins, leukotrienes, and PAF, all of which can influence gastrointestinal motility (5,16). Furthermore, in sensitized rats, intestinal luminal challenge with egg albumin produces diarrhea and significant changes in intestinal myoelectrical activity (17), and mast cell degranulation induces changes in colonic motility through 5-HT₃ receptor activation (18). Such immediate and extensive responses suggest that extensive enteric nerve circuitry has been activated by mast

cell degranulation. Our data suggest that the underlying mechanism in humans is similar.

Although the ingestion of cow's milk proteins produce immunologically mediated adverse reactions in 2.5% of young infants (2), and although regurgitation and vomiting are among the commonest manifestations of such reactions, it appears that food allergy often is not immediately recognized as the cause of these symptoms, and a diagnosis of primary GER (i.e., reflux due to delayed maturation of the so called anti-reflux barrier and especially of the lower esophageal sphincter) is initially made. In a recent study, 42% of 204 infants thoroughly evaluated for symptoms of GER were shown to have CMPA as the underlying cause of their reflux symptoms (4). Either after the failure of a conventional antireflux treatment (postural therapy, thickened food, and prokinetic drugs) or because of supervening complications (e.g., failure to thrive, hematemesis, anemia) many infants and children may then undergo specific investigations, such as upper gastrointestinal endoscopy and intraesophageal pH monitoring.

Paradoxically, however, such investigations may add to the confusion. In fact, biopsy samples taken at endoscopy usually show features such as basal zone hyperplasia, elongation of vascular papillae, and mild eosinophilic infiltration of the epithelium (usually 1–3 cells per high-power field [HPF]), which correlate with prolonged exposure to acid of the esophageal mucosa as measured by 24 hour pH monitoring and are thus considered to be histologic evidence of acid GER disease, both in children and adults (19–21). The finding of a higher number of eosinophils (>10 cells/HPF) in the esophageal mucosa of children with dysphagia and vomiting suggests that true eosinophilic (thus, possibly allergic) esophagitis exists (3,22).

There is still uncertainty about whether the eosinophilic inflammation of the lower esophagus may be responsible for impaired lower esophageal sphincter function and thus true secondary GER. This would probably be the case if eosinophils could be seen within the muscularis mucosa, but biopsy samples taken at endoscopy are too superficial to verify that. It is interesting, however, that infants with regurgitation and vomiting related to CMPA seem to have a characteristic cyclic pattern of postprandial acid reflux episodes at prolonged intraesophageal pH monitoring (23).

In conclusion, in infants with vomiting due to CMPA, a cow's milk meal results in gastric dysrhythmia and delayed gastric emptying which may exacerbate GER and induce reflex vomiting. Electrogastrography and the measurement of gastric emptying of a cow's milk meal may therefore be used as an alternative to other invasive or noninvasive tests (i.e., prolonged intraesophageal pH monitoring (23) and intestinal permeability test with cellobiose and mannitol (24)) to discriminate between vomiting due to primary GER and vomiting due to CMPA, especially when the symptoms are not very evident dur-

ing challenge. The dysfunction of the enteric neuromusculature underlying gastric dysrhythmia and delayed gastric emptying in vomiting infants with CMPA is probably mediated by the local release of histamine, serotonin, and other polypeptides.

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