

Severe Gastroesophageal Reflux Disease and Cow Milk Hypersensitivity in Infants and Children: Disease Association and Evaluation of a New Challenge Procedure

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) and cow milk hypersensitivity are frequent disorders of infancy. A possible causative association between these two entities has been suggested.

Objective: The primary aim was to elucidate whether a causative relationship between the two entities could be established in a population of infants and children. A secondary aim was to evaluate whether cow milk challenge during esophageal pH monitoring is useful as an objective method to identify this subgroup of patients.

Methods: Upper endoscopy followed by a 48-hour esophageal pH monitoring with cow's milk elimination diet at day 1 and challenge at day 2. Cow milk hypersensitivity was later verified by elimination diet and a second open (in patients <3 years of age) or double-blind placebo-controlled (in patients ≥3 years of age) challenge. Skin prick test, specific serum immunoglobulin E and skin patch test were used as supplementary procedures.

Follow-up endoscopy and pH monitoring were performed after 3 months of treatment (omeprazole versus elimination diet dependent on evidence of food hypersensitivity).

Results: Eighteen of 42 investigated patients had severe GERD, defined as endoscopic esophagitis and/or a reflux index >10%. Among these patients, a group of 10 patients with GERD and cow milk hypersensitivity was identified. This group had a significantly higher reflux index compared with children with primary GERD. No significant increase was noted in reflux index during simultaneous pH monitoring and milk challenge.

Conclusions: An association between GERD and cow milk hypersensitivity was observed in both infants and children with severe GERD. Simultaneous cow milk challenge and pH monitoring had limited value as a method to identify this subgroup.

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INTRODUCTION

Gastroesophageal reflux disease (GERD) and food hypersensitivity are frequent disorders of infancy. Cow milk allergy/intolerance is the most common form of food hypersensitivity in infancy (1). Clinical tolerance to cow milk frequently develops during the first few years of life. GERD also has a marked tendency towards spontaneous improvement during the first years of life, probably as a result of changes in feeding habits, growth and improved function of the lower esophageal sphincter (2–

4). The major pathophysiologic mechanism of GERD in both infants and older children is spontaneous transient lower esophageal sphincter relaxation (5). Recent results suggest a causative association between GERD and food hypersensitivity (6–10). The GERD-cow milk hypersensitivity (CMH) association has primarily been described in infants and toddlers. Variable prevalences of CMH in infants with GERD have been reported (6–10). In one study CMH was identified in 82 of 204 (42%) infants with GERD (6). This association is far beyond what can be expected from pure coexistence of the two common entities, as recently stated in a review by Salvatore and Vandenplas (11). Different diagnostic criteria for GERD (endoscopy, histology and esophageal pH monitoring) may partly explain this variation, as the overall correlation between these different diagnostic modalities remains poor (12,13). In addition, different diagnostic criteria for cow milk allergy may contribute to the discrepancies between these studies. A revision of the nomenclature for adverse reactions to food has recently

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been proposed (14). Food hypersensitivity was defined as an adverse reaction to a specific food antigen. The reactions were classified into food allergy (immunoglobulin E and non-immunoglobulin E mediated) and non-allergic food hypersensitivity (previously named intolerance) based on evidence of an immune mediated reaction. Several questions regarding the causal relationship and the optimal diagnostic modalities of the GERD-CMH association remain unsolved.

In the present study we chose strict diagnostic criteria for GERD and CMH. The objectives were to determine whether an association between GERD and cow milk allergy/hypersensitivity could be identified in infants and older children, to examine whether cow milk challenge performed during esophageal pH monitoring could be used as an objective test to identify the GERD-CMH subgroup and to determine whether any specific endoscopic or pH metric findings were characteristic of the GERD-CMH subgroup. Finally, we evaluated the effect of elimination diet on reflux parameters in this subgroup of patients.

SUBJECTS AND METHODS

During a 2-year period all infants and children (0–15 years) with symptoms of GERD and without any previous diagnosis

of food hypersensitivity admitted to the Department of Paediatrics, Odense University Hospital were prospectively included in the project algorithm (Fig. 1). Infants/children with known causes of GERD, such as malformations/atresia of the esophagus and neurologic impairment, were excluded. Cases of lactase deficiency (level of brush border enzymes evaluated in all patients) and *Helicobacter pylori* gastritis (biopsy) were excluded. A total of 51 patients fulfilled the inclusion criteria; 45 accepted inclusion (median age, 105 months; range, 1 to 180 months). Three patients were excluded during the initial pH monitoring. Two were unable to complete the second recording day and in one case, malfunction of the pH monitoring equipment occurred. A total of 42 patients completed the initial diagnostic procedures for GERD and CMH.

Endoscopy

Upper endoscopy was performed under general anesthesia using an Olympus Gif N230 videoscope (Ballerup, Denmark). Endoscopic esophagitis was classified according to the Los Angeles classification, Grade A–D (15). Findings that might indicate food hypersensitivity, such as duodenal nodules, were noted. Biopsies were performed in conjunction with the endoscopy. Histological criteria for GERD were not used in this study.

pH Monitoring

The Digitrapper MK III (Medtronic A/S, Skovlunde, Denmark) monitor was used in nine patients with a disposable

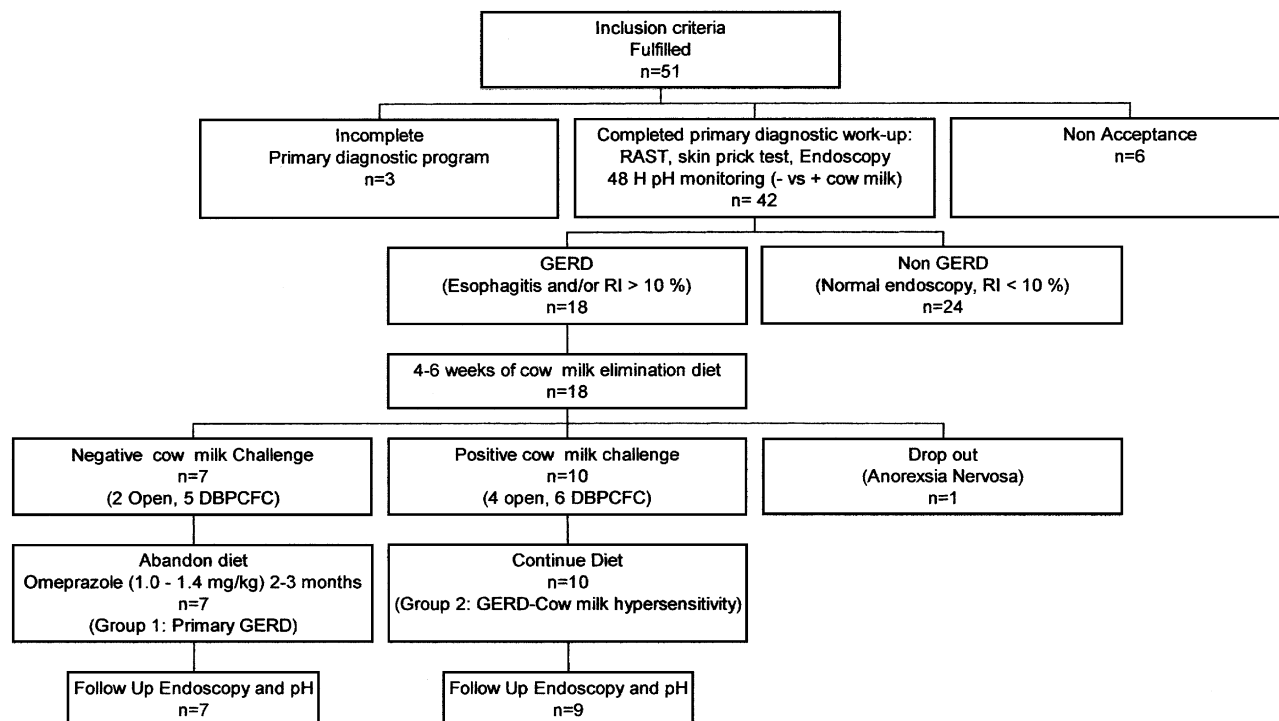


FIG. 1. Project algorithm: Cow milk elimination diet was initiated in all infants and children ($n = 18$) fulfilling the project criteria for severe gastroesophageal reflux disease (reflux index $>10\%$ and/or endoscopic esophagitis). After 4–6 weeks of cow milk elimination diet an open (in patients <3 years of age) or double-blind placebo-controlled cow milk challenge (in patients >3 years of age) was performed. An association between gastroesophageal reflux disease and cow milk hypersensitivity was confirmed in 10 of 17 patients (Group 2) whereas seven had a negative challenge and were classified as primary GERD (Group 1). Follow-up endoscopy and pH monitoring was performed after 3 months of treatment.

one-channel antimony pH probe endoscopically placed 3 cm above the lower esophageal sphincter. The Digitrapper pH (Medtronic) was used in the remaining 33 patients. A disposable two-channel antimony pH probe with 10 cm of spacing was placed according to the endoscopically defined distance to the lower esophageal sphincter. The upper channel was placed 3 cm above and the lower channel approximately 5–6 cm below the lower esophageal sphincter depending on the length of the lower esophageal sphincter. If the precise probe placement was questionable, the position was controlled endoscopically. The equipment was calibrated before use according to manufacturer guidelines. Esophageal and gastric pH were recorded for a period of 48 hours with both recording systems. During the first 24 hours the infant or child was kept on cow milk elimination diet and during the second recording day an open cow milk challenge was performed. Dose depended upon age: infants/children below 3 years of age received a minimum of 5, 10, 20, 40 and 80 ml of cow milk at 2-hour intervals. Children older than 3 years of age received 5, 10, 40, 80 and 160 ml of cow milk at 2-hour intervals. This initial challenge was not used for classification of allergic status but only for evaluation of changes in reflux index (RI) during milk ingestion. No patients received medical anti-reflux therapy or elimination diets before the initial diagnostic work-up.

The following parameters were analyzed: RI (the fraction of time with pH <4 in the esophagus), number of reflux episodes (esophageal pH <4 for a minimum time of 15 seconds), long reflux episodes (longer than 5 minutes), longest reflux episode (minutes) and postprandial reflux index (within 2 hours after meals). Sub-analysis was performed of the postprandial hours after milk ingestion (five times over a 2-hour period). The RI was used as the main reflux parameter. Median gastric pH and fraction of recording time with gastric pH <4 were calculated for the 33 patients who underwent the Digitrapper pH studies including gastric pH measurement. From the gastric data the "adjusted RI" was calculated by the following formula: $((\% \text{ time with esophageal pH } <4 / \% \text{ time with gastric pH } <4) \times 100)$, thereby adjusting the RI for the extent of gastric buffering time. The individual pH recordings were evaluated for day-to-day changes in RI. We have previously evaluated the reproducibility of esophageal pH monitoring (16). The results from this previous study were used as set point for the physiologic day-to-day variations in RI. The limits of agreement for RI at day 2 were calculated to be a factor 0.19 to 3.3 times the initially obtained value at day 1.

Project Algorithm

Project criteria for severe GERD were defined as endoscopic esophagitis (Los Angeles grade A or above) and/or a RI >10% on at least one of the two recording days (although the average RI during 48 hours could be <10%). Cow milk elimination diet was initiated in all infants and children fulfilling these criteria (Fig. 1).

Food Challenges

A second cow milk challenge, used for classification of allergic status, was performed after a diet period of 4–6 weeks. Double-blind placebo-controlled food challenge was performed in children above 3 years. Challenges were performed according to EAACI guidelines (17,18). Cocoa was used as an addi-

tive to avoid differences in flavor between the two challenge preparations (active = milk versus placebo = soy milk). Infants and children below 3 years of age were challenged by an open procedure. The same doses of cow's milk given at the initial challenge were applied but this time at 15-minute intervals as recommended by EAACI. An observational period of 2 hours followed the challenge. The challenge code was not broken until 48 hours after the second challenge to enable classification of late reactors.

Reactions were classified according to gastrointestinal and/or extra-intestinal involvement (skin and upper/lower airway). Reaction time and dose were noted. Allergic status used for classification of GERD groups was based on this elimination/challenge procedure and not on the initial open challenge during pH monitoring. If this second challenge was negative primary GERD was diagnosed and omeprazole treatment was initiated (1.0–1.4 mg/kg) for a period of at least 3 months (Group 1). If positive, the association of GERD and CMH was confirmed and the infant/child continued cow milk elimination diet for at least 3 months until follow-up (Group 2).

Supplementary Allergological Diagnosis

Skin prick test was performed by the prick-by-prick method using fresh foods: cow milk, hen's egg, soy, wheat, fish (cod) and peanuts. A wheal of at least 3 mm in diameter was regarded as a positive reaction. Histamine dihydrochloride (10 mg/ml) was used as positive and allergen dilution as negative controls.

The 17 infants/children with severe GERD underwent skin patch tests for milk and egg; 20 μ L of cow milk and mixed hens egg were added to blotting/filter paper and occluded by aluminium cups (12 mm Finn Chambers, Alapharma A/S, Norway) on uninvolved skin at the upper part of the back. Scanpor tape (Norgesplaster, Alapharma A/S, Norway) was used for fixation. Occlusion time was 48 hours. Evaluation was performed at 20 minutes and 48 and 72 hours and erythema, micropapules and vesicles were noted by a three-step grading system (19). Serum levels of specific immunoglobulin (Ig) E (RAST method, MagicLite/ALK-Abello) were determined for cow milk, hen's egg, soy, wheat, fish (cod) and peanuts. RAST class 2 (> 4 SU/mL) or above was regarded as a positive test. The total amount of serum IgE and eosinophils in blood were measured.

Follow-Up

Follow-up was conducted 3–4 months after the elimination/challenge procedure for Group 1 (primary GERD) after omeprazole treatment and after continuous elimination diet for Group 2 (GERD-CMH). Endoscopy and pH monitoring were repeated for a total of 16 children.

Ethics

The protocol was approved by the Regional Committee for Ethics in Medical Research for Vejle and Funen Counties, Denmark. Informed consent was obtained from parents or legal guardians.

Statistics

Data are presented as median and range. Bar charts for reflux parameters are shown with bar height representing the median

and error bar the 75th percentile. Groups were compared by the Mann-Whitney *U*-test and Fisher's exact test when appropriate. Paired data were analysed by the Wilcoxon signed rank test. *P* values <0.05 were regarded as significant.

RESULTS

Classification of GERD Patients

Based on the project criteria 18 infants/children (median age, 104 months; range, 2 to 178 months) with severe GERD were identified. Seven infants/children were included because of endoscopic esophagitis (LA grade A, 4; grade B, 1; grade C, 2). The remaining 11 infants/children were included because of RI >10% on at least one of the two recording days. A total of 24 infants/children did not meet these criteria and served as controls.

Double-blind placebo-controlled food challenge was performed in 12 patients (median age, 128 months; range, 83–178 months) and open challenge in six patients (median age, 15 months; range, 2 to 30 months). Eight challenges were negative (two open and six blinded challenges). Ten challenges were positive (4 open and 6 blinded challenges). Two cases of placebo (soy milk) reactions occurred during the blinded procedures. In one of these children an additional blinded challenge was proved a negative result for both cow milk and soy milk. This child was therefore classified as non-allergic. The other child, a girl 12 years of age, was excluded as a result of the development of anorexia nervosa. These data yield an overall GERD-cow milk hypersensitivity association of 59% (10 of 17). No age differences were noted between the GERD groups. Follow-up pH monitoring was conducted for 16 infants/children, seven in Group 1 (after omeprazole treatment) and nine in Group 2 (after elimination diet). One patient was lost to follow-

up on parental demand after their infant's GERD symptoms completely resolved on cow milk elimination diet. Thirteen of the 16 infants/children accepted a repeated 48-hour esophageal pH monitoring with simultaneous cow milk challenge as performed at the initial investigation. Three children accepted endoscopy and pH monitoring but refused further cow milk ingestion. In these cases pH was recorded for 24 hours. Patient flows are summarized in Fig. 1.

Reaction Type, Time and Dose

In all cases the reaction type was identical with the symptoms that initially resulted in referral for endoscopy. Reaction time and dose are summarized in Table 1.

Allergological Characterization

In Group 1 (Primary GERD) none were skin prick test positive. In Group 2 (GERD-CMH) one was positive to milk, soy and peanut. All these food antigens were eliminated and the second challenge was performed with cow milk. Two skin prick positive patients were observed (soy = 1, milk and egg = 1) in the control group (*n* = 24).

No differences were found between the groups with regard to levels of serum-IgE (Group 1 median 14.5 SU/mL, range 2–145 SU/mL versus Group 2 median 10.0 SU/mL, range 2–810 SU/mL) or specific IgE antibody levels.

Skin patch test was performed in the 18 patients with GERD. Of the ten patients with the GERD-CMH association five exhibited grade 1 erythema upon the 48-hour evaluation and four also at the 72-hour evaluation (one child was not available for assessment at 72 hours). No cases of micropapules or vesicles were noted. No skin reactions were noted in the primary GERD group.

TABLE 1. Characteristics of the 10 infants/children with the GERD-Cow milk hypersensitivity association

Patient	Age (months)	Sex	RI (48-h)	Esophagitis (LA)	Challenge type	Reaction type	Time	Dose (ml)	Skin prick test	Patch test	RI follow-up
1	20	M	25.00	0	Open	Distress, vomiting, diarrhea	10 H	295	–	–	18.20
2	157	M	7.65	A	DBPCFC	Abdominal pain, and heartburn	5 min	5	–	+	9.50
3	124	M	16.20	0	DBPCFC	Abdominal pain and heartburn	14 H	295	–	+	18.85
4	14	M	32.90	C	Open	Regurgitation, vomiting	30 min	55	+	+	28.85
5	131	M	13.30	0	DBPCFC	Abdominal pain and heartburn	1 H	265	–	–	10.65
6	103	F	23.10	0	DBPCFC	Heartburn	1 H	216	–	–	6.60
7	2	M	15.60	0	Open	Regurgitation, Stridor, distress	2½ H	155	–	–	Lost to follow-up
8	166	M	14.75	0	DBPCFC	Heartburn, nausea	1½ H	295	–	+	9.60
9	16	M	8.65	0	Open	Diarrhea, distress	2 days	155	–	+	10.75
10	106	F	8.60	0	DBPCFC	Heartburn, nausea	45 min	135	–	–	4.90

Time and dose are expressed from start of challenge until a clinical reaction occurred.

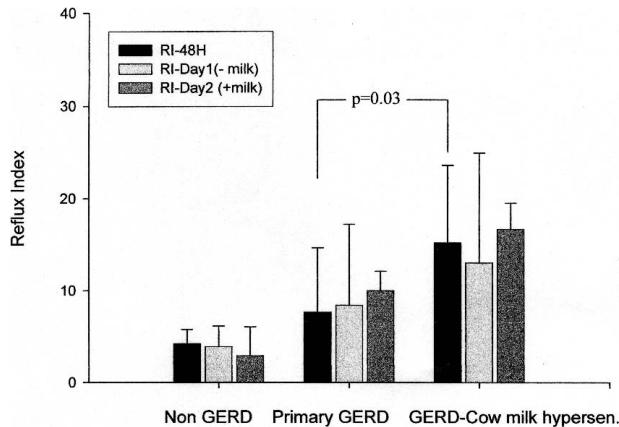


FIG. 2. Reflux index at primary diagnostic evaluation. A significant difference was observed between the Primary GERD and the GERD-Cow milk hypersensitivity group ($P = 0.03$) for the 48-hour recording. No statistically significant differences between the two recording days (– versus + milk) were observed for any of the groups. Bars denote median value (error bars represent 75th percentile)

pH Monitoring in GERD Patients: Initial pH Recording

Based on the total 48 hours of recording time the patients in Group 2 (GERD-CMH) showed a significantly increased time of esophageal acid exposure (Fig. 2) compared with Group 1 (GERD); $P = 0.03$. This difference was not the result of an increased number of reflux episodes but of longer reflux episodes, as shown by a significantly larger number of reflux episodes lasting longer than 5 minutes. ($P = 0.01$; Fig. 3). The pH recordings were subdivided into two 24-hour periods: day 1 (cow milk elimination diet) and day 2 (open cow milk challenge). No significant differences in RI from day 1 to day 2 were noted for any of the groups (Table 2). Likewise, no significant differences between groups

were observed for the following parameters: postprandial RI (defined as RI after any meal, time limit 120 min), postprandial RI – after milk challenge (defined as five times over a 2-hour period after milk ingestion on day 2 compared with the same time period on day 1), median gastric pH values or the fraction of recording time with gastric pH <4. Adjusting the RI for the fraction of time with gastric pH >4 with no acid available for detection did not change these characteristics (Table 2). A phasic pattern with a progressive postprandial decline in esophageal pH was observed in two infants from the 10 patients in Group 2. Notably, both infants exhibited the phasic pattern on both recording days including feedings without cow milk protein. The pattern was continuous throughout the day (Fig. 4A). None of the seven primary GERD or 24 control patients showed the phasic pattern.

Follow-up pH Recording

A significant reduction in the RI (total recording time) was observed in the GERD-CMH group after elimination diet period (Group 2 median RI at the initial recording: 15.6 (range, 7.7 to 32.9) and at follow-up: 10.7 (range, 4.9 to 28.9), $P = 0.05$). No significant changes were noted in Group 1 (Primary GERD) median RI at initial monitoring: 7.7 (6.2–23.5) and at follow-up after omeprazole: 4.6 (2.8–20.4), $P = 0.12$. As for the initial pH recordings no statistically significant difference in the RI was observed for any of the groups between the two recording days.

Day-to-day Variability

The 42 initial and 13 follow-up pH recordings with simultaneous cow milk challenge at Day Two were analyzed individually. Three children showed an increased RI at cow's milk challenge beyond the level of day-to-

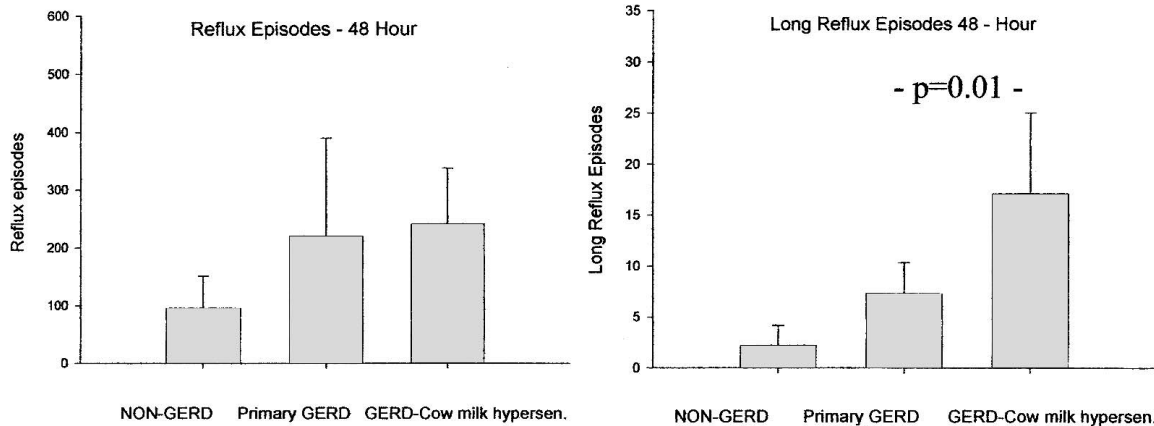


FIG. 3. Reflux episodes and long reflux episodes in the different groups. The increased level of reflux index noted at 48 hours pH monitoring in the GERD-cow milk hypersensitivity group was induced by significantly larger number of long reflux episodes (>5 min). Bars denote median value (error bars represent 75th percentile)

TABLE 2. Reflux parameters for the primary GERD and GERD-Cow milk hypersensitivity group

	GERD		GERD-Cow milk hypersensitivity		<i>P</i> value between groups (48-h)
	Day 1 (– milk)	Day 2 (+ milk)	Day (– milk)	Day 2 (+ milk)	
Reflux Index—48-h (median)		7.7		15.6	0.03
Postprandial meal (time limit: 120 min)		13.9		14.9	NS
Postprandial milk (Day 2, 5 × 2 hours)		18.0		18.9	NS
Reflux Index—Day 1 versus Day 2 (median)	8.4	10.0	14.0	17.5	
Median gastric pH	1.9	2.4	2.1	2.4	NS
Fraction of time with gastric pH < 4 post milk* vs. same time period at day one	74.3	76.3*	79.9	81.4*	NS

P value between days was not significant for all categories.

day variability (upper limit = 3.3), one in the non-GERD/control group with RI 0.1 (day 1) to 1.2 (day 2), one in the primary GERD group (2.8 to 9.2) and one in the GERD-CMH Group (3.1 to 16.0).

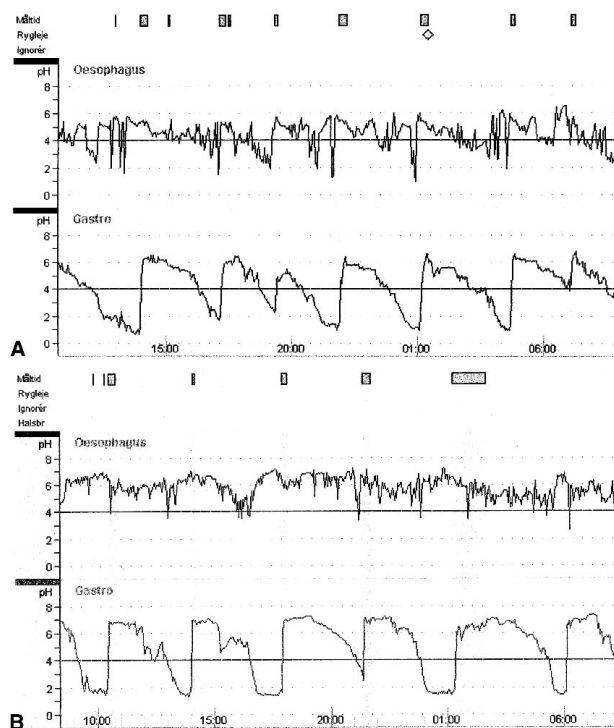


FIG. 4. **A**, dual pH trace (esophageal and gastric recordings) from an infant at age 2 months with cow milk hypersensitivity and gastroesophageal reflux disease (reflux index, 15.8%). A clear phasic pattern is present in the stomach with projection of the pattern into the esophageal recordings. Mealtimes are marked as grey zones. **B**, a dual pH trace from a normal infant at age 4 months. Feeding times with cow's milk formula are noted as grey areas. A profound buffering effect upon gastric pH is noted producing the characteristic phasic pattern in the gastric recording. The esophageal trace is normal (reflux index, 1.0%).

Endoscopic Findings

At primary endoscopy seven patients had esophagitis (Group 1, *n* = 4 and Group 2, *n* = 2). One was later excluded as described above. At follow-up esophagitis had completely resolved in three patients, was reduced in one patient (Grade C to Grade A) and was unchanged in one patient (Grade C). In addition we found one new case of esophagitis (Grade A). The endoscopies were evaluated for the presence of lymphoid nodules in the duodenal bulb. Lymphoid nodules were observed in a total of five cases, one of 24 infants/children without severe GERD, none in the seven with primary GERD and four of 10 infants/children with GERD-CMH, (Fisher's exact test, *P* = 0.01). At follow-up endoscopy after diet treatment the nodules had resolved in three of four infants/children in the GERD-CMH group.

DISCUSSION

In the present study, the GERD-cow milk hypersensitivity association was demonstrated in 10 of 17 patients with severe GERD using strict criteria for both GERD and food hypersensitivity. No significant differences in RI were observed between the two recording days ($\pm$ cow milk) at the initial procedure (without previous diet) or at the follow-up investigation (after a diet period). This result limits the diagnostic yield of a simultaneous food challenge and esophageal pH monitoring procedure.

Food challenges are usually performed with increasing doses of the allergen at short time intervals of 15 to 30 minutes (17). In the present study the initial challenge was performed in conjunction with esophageal pH monitoring. Administration of cow milk at 2-hour intervals was used to enable detection of a phasic pH pattern in the esophagus after meals and to avoid reflux episodes induced by transient lower esophageal sphincter relax-

ations resulting from gastric distension. The so-called phasic pH pattern may be defined by an abrupt mealtime-related increase in esophageal pH followed by a gradual decline towards the next meal. In our study such a phasic pH pattern was noted in only two cases of GERD-CMH. Both infants exhibited the pH pattern at both recording days ($\pm$ cow milk). These data are at variance with previous reports of the phasic pH pattern as a characteristic feature of the GERD-CMH association (10,20). Others have also reported very few (9) or no (21) cases of this pattern among GERD-food hypersensitive children. However, the phasic pH pattern was in the present study observed in gastric pH recordings among infants (Fig. 4B), where it clearly represents a normal physiologic phenomenon as a result of the intermittent buffering effect of meals. The precise location of the pH probe is important in the evaluation of this pattern, as displacement or later dislocation towards a more distal position will not only increase the RI but also produce the phasic pH pattern, especially in infants because of their lower gastric buffering capacity. Several studies have used the formula of Strobel et al. (22) for probe placement. In the present study the pH probe was placed according to visual endoscopic measurement and the phasic pH pattern was not characteristic of the GERD-CMH association.

The methodology used in the present study calls for consideration of several factors. We used a dual pH probe that measured simultaneous gastric and esophageal pH. A purpose of this feature was to elucidate whether ingestion of cow milk during day 2 recording induced a buffering effect on gastric pH exceeding the buffering capacity of the ingested food at day 1. No differences between the two recording days were seen in the amount of time with gastric pH <4 . Theoretically, a hypoallergenic formula on day 1 would have removed the potential differences in buffering substances in the stomach, but in retrospect this precaution proved unnecessary because of the similarity of the gastric pH data between the two days. The presence of a pH probe across the lower esophageal sphincter may induce a leak and thus influence the esophageal pH recording, a problem that has only been investigated to a limited extent in infants and children. However, tubes of the size at the pH probe used in the present study (2.1 mm) or smaller have been demonstrated to not influence the amount of acid reflux (23). Finally, although the endoscopy and general anesthesia at day 1 might influence the initial part of pH monitoring, others have found this effect to be of minimal importance (24).

Cow milk challenge during esophageal pH monitoring could be potentially valuable as an objective method to identify the GERD-CMH subgroup. It is essential in such studies to use an estimate of the normal physiologic day-to-day variability. Using the Bland and Altman limits-of-agreement method (25) we recently assessed the physiologic day-to-day variation of the reflux parameters, without any dietary intervention. Our data showed that

the 95% probability limits for the RI ranged from a decrease by a factor of 0.19 to an increase by a factor of 3.3 during a second consecutive recording day (16). Thus, in the present study an increase of RI during cow milk challenge at day two by a factor of 3.3 or greater would indicate a difference beyond the level of day-to-day variation. Only three patients exceeded these limits during challenge and only one of these was classified as cow milk hypersensitive. In conclusion, these quite broad limits of agreement of the reflux parameters restrict the value of simultaneous pH monitoring and food challenge or any other interventional study evaluated by consecutive pH monitoring. Interestingly, a significant reduction in RI after the elimination diet period was noted in the GERD-CMH group. Larger patient series are required to confirm this potentially important clinical finding.

Recently, attention has been drawn to an altered clinical spectrum of food allergy in the foregut (26). The data from Kokkonen et al. (27) suggest that duodenal lymphoid nodules/lymphonodular hyperplasia is a distinct endoscopic feature associated with food allergy/hypersensitivity, as lymphoid nodules in the duodenal bulb were seen frequently among infants and children with this condition. In the present study lymphoid nodules in the duodenum were observed in four of 10 patients in the GERD-cow milk hypersensitivity group. The lymphoid nodules disappeared in three of four subjects after the diet period. Thus, the data from this admittedly small patient material support the view that lymphoid hyperplasia is a feature, however nonobligatory, of food hypersensitivity with upper gastrointestinal manifestations.

Allergic esophagitis has been associated with the recently described disease entity eosinophilic esophagitis (28). Endoscopic findings of esophagitis in the upper esophagus associated with esophageal rings and webs are characteristic findings of eosinophilic esophagitis (29), which may be primary or secondary to food hypersensitivity. No patients in the present study showed any of these specific endoscopic findings.

In this study the majority of patients hypersensitive to cow milk were identified only by elimination diet followed by open/blinded challenges. Reactions at challenge were mainly restricted to the gastrointestinal tract. All patients except one had negative results of skin prick tests, and tests for specific IgE and thus showed no evidence of a general IgE-mediated immune reactivity. Skin patch tests could be a potentially useful diagnostic test in patients with non-IgE mediated reactions, as the reactivity in the skin patch test presumably depend on T-cell mediated reactions (30). Several studies suggest a clinical relevance of patch tests in skin prick negative infants/children with challenge proven cow milk allergy (31,32) and in children with mainly gastrointestinal/GERD manifestations of cow milk allergy (33). In the present study five of 10 GERD-CMH patients and none in the primary GERD-group reacted with grade one erythema on patch test for cow milk. None had stronger reactions

than erythema. The patch test reactivity was observed in both infants and schoolchildren.

The results in our patients suggest that the possible allergic mechanisms involved might be of local gastro-intestinal nature. Local immunologic mechanisms within adverse reactions to foods have been indicated to occur in challenge-proven but skin prick test and serum IgE antibody negative patients. In adults food challenge in a segment of the jejunum as evaluated by a double balloon technique induced an increase of luminal histamine and eosinophilic cationic protein levels (34). Other studies have reported increased numbers of cytotoxic TIA-1 positive T-cells (35), local IgE positive mast cells (36) and activated eosinophils (37) in the duodenum. Taken together these studies suggest that the further categorization of food hypersensitive infants or children with mainly gastrointestinal symptoms and negative tests for general IgE sensitization depend on the development of local organ-based diagnostic tests.

In conclusion, an association of cow milk hypersensitivity and severe GERD was observed not only in infants but also in preschool/school children. Simultaneous cow's milk challenge and esophageal pH monitoring did not provide any additional diagnostic value. Further studies are needed to characterize the pathophysiological mechanisms behind the association of GERD and cow milk hypersensitivity, especially the interaction of a possible allergic inflammatory process and the enteric nerve system.

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