Clinical and pH-metric characteristics of gastro-oesophageal reflux secondary to cows' milk protein allergy

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Abstract

Aims—The primary aim was to assess whether there were differences in symptoms, laboratory data, and oesophageal pH-metry between infants with primary gastro-oesophageal reflux and those with reflux secondary to cows' milk protein allergy (CMPA).

Patients and methods—96 infants (mean(SD) age 7.8(2.0) months) with either primary gastro-oesophageal reflux, reflux with CMPA, CMPA only, or none of these (controls) were studied. Symptoms, immunochemical data, and oesophageal pH were compared between the four groups and the effect of a cows' milk protein-free diet on the severity of symptoms was also assessed.

Results—14 out of 47(30%) infants with gastro-oesophageal reflux had CMPA. These infants had similar symptoms to those with primary gastro-oesophageal reflux but higher concentrations of total IgE and circulating eosinophils ($p < 0.005$) and IgG anti- β lactoglobulin ($p < 0.003$). A progressive constant reduction in oesophageal pH at the end of a feed, which continued up to the next feed, was seen in 12 out of 14 patients with gastro-oesophageal reflux secondary to CMPA and in 24 of 25 infants with CMPA only. No infants with primary gastro-oesophageal reflux and none of the controls had this pattern. A cows' milk protein-free diet was associated with a significant improvement in symptoms only in infants with gastro-oesophageal reflux with CMPA.

Conclusion—A characteristic oesophageal pH pattern is useful in distinguishing infants with gastro-oesophageal reflux associated with CMPA.

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Gastro-oesophageal reflux can be considered a physiological condition in the first 12 months of life.¹ In some patients, however, gastro-oesophageal reflux can cause both oesophagitis² and respiratory symptoms³ and it has been suggested that it may also lead to apnoeic episodes (apparent life threatening events).⁴ In order to treat pathological reflux a distinction between primary and secondary forms must be

made. It has been suggested that gastro-oesophageal reflux can be secondary to food allergy,⁵ and in our experience the association between gastro-oesophageal reflux and cows' milk protein allergy (CMPA) is very frequent in infants < 1 year old.⁶ We have observed that patients with gastro-oesophageal reflux secondary to CMPA, present a 24 hour pH-metric tracing with a characteristic pattern, and this may help to classify cases as secondary or primary gastro-oesophageal reflux.

The aims of the present study were: (A) to record the frequency of the gastro-oesophageal reflux + CMPA association; (B) to observe eventual differences in the clinical manifestations and laboratory data in patients with gastro-oesophageal reflux + CMPA and in patients with gastro-oesophageal reflux only; (C) to evaluate the pattern of the pH-metric tracing and if it can help in distinguishing between primary gastro-oesophageal reflux and gastro-oesophageal reflux + CMPA; (D) to evaluate the efficacy of a cows' milk protein-free diet in patients with gastro-oesophageal reflux only and those with gastro-oesophageal reflux + CMPA.

Patients

The total study group included 96 consecutive infants (46 boys, 50 girls), mean (SD) age 7.8 (2.0) months (range 1-12), fed with milk formulas containing cows' milk protein, who had been referred to our clinic for observation, and who presented clinical signs or symptoms compatible with a diagnosis of gastro-oesophageal reflux and/or CMPA. We therefore considered those subjects with vomiting, regurgitation, retarded growth, anorexia (refusal to feed), prolonged fits of crying, repeated episodes of bronchospasm, sideropenic anaemia (haemoglobin concentration < 90 g/l), apnoeic episodes.

All the patients underwent 24 hour oesophageal pH monitoring and those with gastroenterological symptoms also underwent endoscopy of the upper gastrointestinal tract. All patients were then placed on an elimination diet without cows' milk and its derivatives, using a milk formula based on hydrolysed casein, and those patients with improved symptoms on the cows' milk protein-free diet underwent a double blind milk challenge, 6-8 weeks later. In accordance with the diagnostic criteria for CMPA,⁷ an intestinal biopsy at the Treitz ligament was performed both before and 24 hours after the challenge in these patients.

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The following patients were considered to have gastro-oesophageal reflux: (A) those with endoscopic evidence of oesophagitis, confirmed histologically by biopsy of the oesophageal mucosa; (B) those where there was a clear link between the observation of the clinical symptom (apnoea or episode of bronchospasm, fits of crying) and an episode of oesophageal reflux recorded during the 24 hour pH monitoring.

Patients were considered to have CMPA if symptoms improved during the cows' milk protein-free diet and cows' milk protein challenge was positive, without considering whether or not there was a coexistent gastro-oesophageal reflux. Figure 1 summarises the study design.

On the basis of the endoscopic findings and cows' milk challenges, we were able to classify our patients into four groups: 33 patients (18 males, 15 females) with primary gastro-oesophageal reflux not associated with CMPA (group 1); 14 patients (seven males, seven females) with gastro-oesophageal reflux associated with CMPA (group 2); 25 patients (11 males, 14 females) with CMPA, without gastro-oesophageal reflux (group 3); and 24 patients (10 males, 14 females) without either gastro-oesophageal reflux or CMPA (group 4). The final diagnosis in patients in group 4 was: coeliac disease (one case), recurrent bronchopneumonia (12 cases), habitual vomiting (six cases), central apnoea (two cases), intermittent stomach volvulus (one case), and cystic fibrosis (two cases).

There was no significant difference between the four groups with respect to age and sex.

At first observation, clinical history was carefully recorded and a scoring system was used to evaluate the severity of the symptoms of the infants admitted to the study, according to our previous studies (see table 1).^{8,9} The same score was used after six weeks of cows' milk protein-free diet to evaluate the effects of the diet in the patients with gastro-oesophageal reflux + CMPA and those with gastro-oesophageal reflux only.

The parents of the patients gave their informed consent on recruitment of the infants to the study; the study was approved by the ethics review committee of the Institute of Internal Medicine.

Figure 1 Study design (CM(P) = cows' milk (protein), GOR = gastro-oesophageal reflux).

Table 1 Scoring system used to evaluate the children admitted to the trial

		Score
Vomiting and regurgitation (bouts/week)	0	0
	1 - 3	3
	4 - 7	6
	> 7	9
Anorexia or refusal to feed (% requirement/day)	- 5 - 10	0
	- 25	2
	- 50	4
	- 75	8
Pyrosis, fits of crying (bouts/week)	0	0
	1 - 3	2
	4 - 7	4
	> 7	6
Ratio weight/height (centiles)	> 35	0
	34 - 10	3
	9 - 5	6
	< 5	9
Haemoglobin (g/l)	80 - 90	2
	70 - 79	4
	< 70	6

Methods

OESOPHAGEAL ENDOSCOPY

Patients with gastroenterological symptoms underwent upper gastrointestinal endoscopy, performed with a standard forward viewing paediatric fibroscope. The diagnosis of oesophagitis and the classification of its severity were based on an endoscopic and histological examination of the oesophagus, as in our previous studies.^{8,9}

24 HOUR PH MONITORING

pH monitoring was performed by passing a flexible miniaturised electrode with a pH sensitive tip through the nose and along the oesophagus, where it was positioned at a point equal to 87% of the nose-lower oesophageal sphincter distance, calculated using the formula of Strobel *et al.*¹⁰ The technique of standardisation, the apparatus used, and the method of recording were the same as those already described in our previous studies.^{8,9} At the end of the monitoring period the computer provided numerical data relative to the following indices: (A) monitoring time, (B) reflux episode time, (C) percentage and length of time during which pH was less than 4, (D) number of reflux episodes, and (E) duration of the longest single reflux episode.

GRAPHIC INTERPRETATION OF THE PH TRACING

The whole tracing was evaluated. A pH tracing usually shows a baseline and oscillations in pH that are more or less marked and rapid, without any definite rhythm. In our experience, in contrast, patients with gastro-oesophageal reflux secondary to CMPA had a characteristic pattern trace: there is a progressive, gradual, and slow decrease in intraoesophageal pH, starting from the immediate postprandial phase and continuing in the next three hours, until a further meal causes an increase in pH towards baseline values. This constant trend over the 24 hours eventually produces a tracing with a phasic pattern, regulated by the number of feeds per day.

During the study, the pH-metric tracings were classified as 'phasic' or 'non-phasic', immediately after recording; at this moment we did not know either the result of the cows' milk

protein-free diet or the following challenge. Operators were also blinded as to the clinical history of the patients and the laboratory immunological data.

COWS' MILK CHALLENGE AND INTESTINAL HISTOLOGY

After 6–8 weeks of a cows' milk protein-free diet, the patients were recalled and those who had shown an improvement in symptoms were challenged with cows' milk protein. The challenge was performed by administering a formula containing cows' milk protein or a semielemental formula, beginning with an initial quantity of 10 ml and reaching the total equivalent of a full feed in three hours. Neither the researchers nor the patients knew whether the feed did or did not contain cows' milk protein. When the formula given was then found to be without cows' milk protein, the challenge was repeated over the following days, always double blind, until the patient had received a cows' milk protein formula. Moreover, all the patients underwent a baseline intestinal biopsy before the beginning of the double blind challenges. Twenty four hours after challenge, after determining the clinical reaction, we opened the envelope revealing whether the formula given to the patient contained cows' milk protein or not; when the challenge had actually been made with cows' milk protein the patient then underwent a second intestinal biopsy.

Biopsy specimens were obtained just distal to the ligament of Treitz, as previously described.^{11 12} Specimens were stained with haematoxylin and eosin, and histology was described by an examiner unaware of the clinical reaction to the challenge.

The challenges were considered positive if: (A) the same symptoms that the patients had presented on referral to our department reappeared within 24 hours after challenge and (B) an intestinal biopsy specimen, which was normal before challenge, presented after challenge with partial atrophy of the intestinal villi and lymphocyte eosinophil infiltration of the lamina propria.

OTHER IMMUNOLOGICAL TESTS

On recruitment to the study other laboratory tests for CMPA were also performed in all patients. Cutaneous tests were made using full cream cows' milk, lactalbumin and β lactoglobulin (Lofarma Diagnostic); any weal diameter that exceeded that of the control and was more than one fourth the size of the histamine weal was regarded as positive. Total serum IgE (Phadebas IgE paper radioimmunosorbent test kit, Pharmacia Diagnostics) was considered raised if > 60 Kallikrein units/l. The level of eosinophils in the peripheral blood was positive if these were $> 0.4 \times 10^9/l$; the reference values for the normal limits of all the above tests were obtained in our laboratory on a wide population of healthy subjects in the same age range as the patients. Moreover, IgG anti- β lactoglobulin was assayed (Betalactotest, Eurospital): values $> 36\%$, higher than a control standard (up to 20%), were considered positive; this threshold value had the highest

diagnostic accuracy in a large study performed on over 200 healthy controls and over 200 CMPA patients.¹³

STATISTICAL ANALYSIS

The range and median values were calculated for all the pH-metric and clinical score data we recorded. The Mann-Whitney test was used to compare the various pH-metric indices in the patients with primary gastro-oesophageal reflux and in those with gastro-oesophageal reflux secondary to CMPA. The clinical scores before and after the cows' milk protein-free diet were compared within each group using the Wilcoxon rank sum test. A comparison in scores between patients with gastro-oesophageal reflux only and those with gastro-oesophageal reflux + CMPA was performed using the Mann-Whitney U test both before and after the cows' milk protein-free diet. The χ^2 test was used to determine the frequency of the various symptoms at diagnosis and to evaluate the frequency of patients with primary gastro-oesophageal reflux and those with secondary gastro-oesophageal reflux who presented the characteristic phasic tracing pattern. The same test was employed to analyse the differences in distribution for sex, age, and family history.

Results

Oesophageal endoscopy showed that 47/89 patients had oesophagitis; according to histological findings, it was grade 1 or 2 in 44 and grade 3 in three. The latter three patients were treated with a prokinetic associated with an antacid, while in the other cases only dietary and positional treatment was started.

Although a number of patients were admitted to the study for respiratory problems, there was no evidence in the oesophageal pH monitoring to indicate gastro-oesophageal reflux as the cause of the respiratory disorders.

During the cows' milk protein-free diet period, 44 patients showed a clear improvement in symptoms; these patients were recalled after 6–8 weeks and challenged with cows' milk. Clear symptoms of CMPA emerged during the challenge in 39 patients. All of these intestinal biopsy specimens, obtained before the challenge, showed a normal mucosa, while 24 hours after challenge there was a partial atrophy of the intestinal villi with a lymphoplasmacellular infiltration of the lamina propria in 31/39 patients. In none of the five patients with a negative clinical reaction on cows' milk protein challenge was there any damage to the intestinal mucosa.

Table 2 shows the clinical symptoms at diagnosis in the patients with gastro-oesophageal reflux only and in those with gastro-oesophageal reflux + CMPA. None of the symptoms showed a different frequency in the two groups; however, in 3/14 patients with gastro-oesophageal reflux + CMPA, accurate clinical history revealed concomitant rhinitis or dermatitis.

Table 3 shows laboratory data, recorded at diagnosis. All the immunological tests performed were more frequently positive in

Table 2 Frequency of different symptoms on hospitalisation in patients with gastro-oesophageal reflux alone (group 1) and gastro-oesophageal reflux + CMPA (group 2)

	Group 1 (n = 33)	Group 2 (n = 14)
Vomiting	20	8
Regurgitation	23	10
Growth disorders	6	2
Anorexia (food refusal)	8	2
Fits of crying	8	4
Anaemia	0	1
Dermatitis	0	2
Rhinitis	0	1

Table 3 Number with abnormal immunological tests on hospitalisation in patients with gastro-oesophageal reflux alone (group 1) and with gastro-oesophageal reflux + CMPA (group 2)

	Group 1 (n = 33)	Group 2 (n = 14)
Prick tests	1	7*
Serum total IgE	0	6†
Circulating eosinophils	0	6†
Serum IgG anti-β lactoglobulin	4	13‡

$\chi^2 = 7.35$, $p < 0.01$; †8.37, $p < 0.005$; ‡9.32, $p < 0.003$.

patients with gastro-oesophageal reflux + CMPA; in particular the IgG anti-β lactoglobulin assay was the most sensitive, with values raised in 13/14 cases. Clinical family history showed atopy in the parents or siblings of 5/14 subjects with gastro-oesophageal reflux + CMPA and in 7/33 subjects with gastro-oesophageal reflux alone (difference not significant).

Table 4 shows the main pH-metric indices recorded on first observation. The Mann-

Table 4 Main indices of pH-metry in patients with gastro-oesophageal reflux alone (group 1) and gastro-oesophageal reflux + CMPA (group 2). Values are range (median)

	% Reflux time	No of reflux episodes	Duration of longest reflux episode (min)	No of reflux episodes > 5 min
Group 1 (n = 33)	6-41 (10)	22-151 (62)	7-120 (28)	1-20 (6)
Group 2 (n = 14)	5-40 (11)	24-173 (71)	6-111 (27)	2-18 (6)

Figure 2 (A) Part of a typical 'phasic' pH tracing observed in a patient with gastro-oesophageal reflux + CMPA. (B) Part of a pH tracing without the phasic characteristic observed in a patient with gastro-oesophageal reflux alone. The arrows show times of feeding.

Table 5 Number of patients with a phasic pH tracing in the four study groups: gastro-oesophageal reflux alone (group 1), gastro-oesophageal reflux + CMPA (group 2), CMPA alone (group 3), and controls (group 4)

Group	Phasic	Non-phasic
1 (n = 33)	0	33
2 (n = 14)	12	2
3 (n = 25)	24	1
4 (n = 24)	0	24

Whitney U test did not show any significant difference between the subjects with primary gastro-oesophageal reflux (group 1) and those with gastro-oesophageal reflux secondary to CMPA (group 2) for the pH-metric indices considered.

The 24 hour oesophageal pH monitoring, however, showed a typical phasic pH tracing with a progressive fall in pH during the postprandial hours and a steep rise when food was consumed in 36/89 patients. This type of tracing was observed both in patients with a total percentage reflux time above the normal limits reported in the literature¹⁴ and also in patients with a normal total percentage reflux time over the 24 hours.

Figure 2A shows an eight hour portion of one of these typical tracings in a patient with a high total percentage reflux time. In the same figure (2B) this is compared with a portion of a tracing that has a completely random distribution of reflux periods.

Table 5 shows the number of subjects in each group presenting on diagnosis the characteristic phasic pattern underlined above. The phasic pattern of the tracing appears to be an exclusive feature of the patients with CMPA, whether or not they had gastro-oesophageal reflux disease. In fact, this type of tracing was not observed in any of the non-allergic patients whereas almost all the CMPA patients had the characteristic phasic pattern. The difference in the frequency of the phasic tracing between patients with or without CMPA was highly significant ($\chi^2 = 21.6$, $p < 0.0001$).

Finally, evaluation of the severity of symptoms, on the basis of the score we elaborated, did not show any significant differences at the start of the study (patients with gastro-oesophageal reflux only: range score 7-20, median 14; patients with gastro-oesophageal reflux + CMPA: range score 7-17, median 14). Excluding the three patients on antireflux drug treatment, after six weeks of diet there was a significant improvement in symptoms in the gastro-oesophageal reflux + CMPA patients (range score 0-8, median 4) ($p < 0.05$ Wilcoxon rank sum test) while there was no improvement in the patients with gastro-oesophageal reflux alone (range 6-20, median 14). After the cows' milk protein-free diet, therefore, the severity of symptoms was greater in the gastro-oesophageal reflux only patients than in those with gastro-oesophageal reflux + CMPA ($p < 0.05$, Mann-Whitney U test).

Discussion

The first basic step to take when deciding the optimum treatment of gastro-oesophageal reflux is to distinguish between cases of primary

gastro-oesophageal reflux and gastro-oesophageal reflux secondary to other conditions.⁵ CMPA is one of the recognised causes of secondary gastro-oesophageal reflux, but to our knowledge there is only one study on three patients regarding the gastro-oesophageal reflux and CMPA association.¹⁵ In our experience gastro-oesophageal reflux secondary to CMPA is very frequent in infants < 1 year old, and it was observed in 85/204 cases previously studied.⁶

The present study confirms the high frequency of the gastro-oesophageal reflux + CMPA association, recorded in 14/47 patients with gastro-oesophageal reflux (30% of cases). As the cows' milk protein-free diet alone determines a significant improvement in symptoms in patients with gastro-oesophageal reflux + CMPA, this further supports the hypothesis that the association of these two diseases is not casual, but rather that gastro-oesophageal reflux and oesophagitis may be directly dependent on CMPA.

The clinical presentation of patients with gastro-oesophageal reflux + CMPA did not differ from that observed in those with gastro-oesophageal reflux only. However it must be stressed that in the gastro-oesophageal reflux + CMPA patient group we observed three subjects with typical CMPA symptoms, such as dermatitis and rhinitis. Immunological data and the analysis of the pH-metric tracing appear to be more useful than clinical history in making a correct diagnosis; in fact in patients with gastro-oesophageal reflux + CMPA we observed a higher, statistically significant frequency of positive immunological tests. Above all, serum concentrations of IgG anti- β lactoglobulin proved to be useful, being raised in 13/14 cases of gastro-oesophageal reflux + CMPA, thus confirming the opportunity of using these tests in diagnosing allergic diseases.^{6 16}

The present study also shows that an examination fundamental for gastro-oesophageal reflux diagnosis, 24 hour oesophageal pH monitoring, is also highly useful in distinguishing between the forms of primary gastro-oesophageal reflux and gastro-oesophageal reflux associated with CMPA. In fact, all the patients in whom oesophageal pH gradually decreased between one meal and the next, giving rise to the characteristic phasic pattern, proved to be suffering from CMPA. This typical pattern was not observed in any of the study patients without CMPA. Furthermore, the sensitivity of the analysis of the tracing in the diagnosis of gastro-oesophageal reflux associated with CMPA was also high: 12/14 patients with secondary gastro-oesophageal reflux presented the characteristic phasic tracing. It is important to underline that this phasic pattern was also seen in patients with CMPA but without gastro-oesophageal reflux. In our study population 24/25 patients with CMPA but without oesophagitis had a phasic pattern.

In addition, we confirmed that none of the classic pH-metric indices are useful for distinguishing between cases of primary gastro-

oesophageal reflux and those of gastro-oesophageal reflux secondary to CMPA.^{6 15}

Many questions remain to be answered, in particular on the pathophysiology of antireflux mechanisms in subjects with primary gastro-oesophageal reflux and in those with gastro-oesophageal reflux secondary to CMPA. It would appear that in patients with gastro-oesophageal reflux + CMPA the transitory and inappropriate relaxation of the lower oesophageal sphincter, which is considered to be the main pathogenetic mechanism behind gastro-oesophageal reflux,¹⁷ do not have a fundamental role. In fact, it appears that there is a persistent functional incapacity of the lower oesophageal sphincter, with the result that the intraoesophageal electrode records the progressive postprandial drop in gastric pH.

Further studies using manometry and evaluating gastric emptying would clarify the pathogenesis of gastro-oesophageal reflux secondary to CMPA.

We believe that various useful indications for clinical practice procedure may emerge from this study. It is obvious that in patients with CMPA who do not have gastro-oesophageal reflux-like symptoms, CMPA diagnosis should be made by means of an elimination diet and a successive double blind challenge; there are serious doubts as to the necessity of routinely using intestinal biopsy after cows' milk protein challenge to support the hypersensitivity reaction, according to our experience. In fact, out of 39 cases with a clear and severe clinical reaction to the cows' milk protein challenge, we recorded damage to the intestinal mucosa in only 31 patients (the sensitivity of intestinal biopsy in the diagnosis of CMPA in our study was therefore 79%).

On the other hand, if gastro-oesophageal reflux is one of the possible diagnoses, and thus a 24 hour pH-metry must be performed, the evidence of a typical 'phasic pattern' is an almost absolutely sensitive and specific instrumental index for identifying an association between gastro-oesophageal reflux and CMPA. Furthermore the simple IgG β lactoglobulin assay may be used as a test to confirm a suspected gastro-oesophageal reflux + CMPA association.

In conclusion, this study shows that: (A) during the first 12 months after birth there is a very high incidence of gastro-oesophageal reflux secondary to CMPA; (B) the symptoms of gastro-oesophageal reflux associated with CMPA are the same as those observed in the patients with gastro-oesophageal reflux only, with the exception of a few patients presenting mild typical CMPA manifestations (dermatitis or rhinitis); (C) immunological tests are useful in suspecting an association between gastro-oesophageal reflux and CMPA; (D) subjects with gastro-oesophageal reflux secondary to CMPA present a typical pH monitoring tracing pattern, characterised by a progressive, slow decrease in oesophageal pH between feeds; and (E) after a cows' milk protein-free diet there is a significant improvement in symptoms in the gastro-oesophageal reflux + CMPA

patients but not in those with gastroesophageal reflux only.

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