

Hematemesis in Infants Induced by Cow Milk Allergy

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Cow milk allergy (CMA) is still a common problem in infants and children which involves the GI tract, the respiratory system and the skin. The prevalence of CMA during infancy is estimated to be 2% in developed countries,^{1,2} but data of developing countries are not available. Cow milk allergy is always suspected in infants who suffer from chronic vomiting and/or diarrhea. Cow milk formulas are usually changed to soy formulas or cow milk protein hydrolysate formulas. Gastrointestinal involvement including esophagitis, gastritis and duodenitis is able to induce hematemesis in CMA but there is little available data on patients with CMA-induced hematemesis.³⁻⁵ The objective of this study was to analyze the clinical manifestations, etiologies, endoscopic findings, the histology of the gastrointestinal mucosa, treatments and clinical course in infants who had hematemesis induced by CMA.

PATIENTS AND METHODS

The medical records of in-

SUMMARY This study was conducted in order to analyze the clinical manifestations, the endoscopic findings, the histology of the gastrointestinal mucosa, the treatments and the clinical course in infants who had hematemesis induced by cow milk allergy. The medical records were reviewed retrospectively. The criteria for the diagnosis of CMA included elimination of cow milk formula resulting in improvement of symptoms, specific endoscopic and histologic findings as well as the exclusion of other causes. Twenty-three infants with a diagnosis of hematemesis were analyzed, which included 20 infants with CMA and 3 infants with gastroesophageal reflux disease (GERD). In the CMA group were 12 girls and 8 boys whose ages were 4.3 ± 1.4 months. The onset of vomiting after starting cow milk formulas was 70.6 ± 48.9 days. Gastroduodenoscopy was performed on 15 patients showing erythema, erosion and friability of the gastric mucosa in all patients and lymphoid hyperplasia in the duodenal bulb in 7 patients. Eight patients had mild to moderate eosinophilic infiltration and 5 patients had eosinophilia. Cow milk formulas were changed to other formulas: two children were initially given extensively hydrolyzed casein formulas and later followed by a soy formula, 14 were given a soy formula and 4 were given partially whey hydrolyzed formulas. All patients showed clinical signs of improvement a few days later. Patients that were able to tolerate cow milk were 1.5 ± 0.9 years old. During the follow-up period (2.6 ± 1.8 years after treatment) 4 patients were diagnosed with asthma, 4 patients with chronic respiratory symptoms, 4 patients with constipation and 2 others with food allergies. CMA induced gastritis in infancy may not be classified as eosinophilic gastritis because of the low level of eosinophilic infiltration. The elimination of cow milk and subsequent substitution with a soy formula is the proper management.

infants with a diagnosis of hematemesis from the Department of Pediatrics, Siriraj Hospital, Mahidol University, from 1993 to 2002 were reviewed retrospectively. Infants who had hematemesis due to CMA were selected and analyzed. The diagnosis of CMA was done using

the following criteria: the elimination of cow milk formula resulted in improvement of symptoms; endoscopic and histologic findings ex-

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cluded other possible causes of hematemesis, i.e. esophagitis, gastritis and duodenitis induced by drugs or infection. Evaluation was done by reviewing the medical records in addition to telephone interviews or correspondence with all of the patients' parents. Demographic data, clinical manifestations, investigations, treatments and outcome were collected and analyzed.

RESULTS

Twenty-three infants with a diagnosis of hematemesis which included 20 infants (12 girls and 8 boys) with CMA and 3 infants with

gastroesophageal reflux disease (GERD) were analyzed in this study. The clinical presentations, investigations, treatments and outcome of the individual patients in the CMA group are shown in Tables 1 and 2. All patients had no underlying diseases. The age-range of the CMA patients was 2.5 months to 6 months (4.3 ± 1.4 months). The age of onset of vomiting was 3.1 ± 1.4 months. Thirteen patients had been breast-fed initially and 3 of them were both breast-fed and receiving cow milk infant formula during the episodes of hematemesis. The average age of patients starting cow milk infant formula was 20.8 ± 26.3 days and 11

patients were fed cow milk in the first week of life. The onset of vomiting occurred 70.6 ± 48.9 days after starting cow milk formula. The duration of hematemesis before diagnosis was 18.8 ± 18.3 days.

Other symptoms included infantile eczema in 1 patient, recurrent mild diarrhea in 5 patients, and frequent respiratory symptoms in 11 patients. Complete blood counts revealed 5 patients had anemia and 5 had eosinophilia (> 500 cells/mm³). Fifteen patients (75%) had gastro-duodenoscopy performed which revealed normal appearance of the esophageal mucosa, but erythema,

Table 1 Clinical data of infants with cow milk induced gastritis

Case	Sex	Age (m)	Onset of vomiting (m)	Duration of vomiting (days)	Duration of hematemesis (days)	Onset after starting cow milk (days)	Diarrhea	Respiratory symptom	Anemia	Eosinophilia
1	F	4	2	60	3	30	-	+	-	-
2	F	2.5	2.5	5	5	45	-	+	-	-
3	F	4	1	90	7	7	-	-	-	-
4	M	3	3	7	7	90	-	+	+	-
5	M	2.5	2	15	5	60	-	+	-	+
6	F	5	1	120	30	30	-	+	-	-
7	M	3	2	60	7	60	-	+	-	-
8	M	5	4.5	14	14	75	+	-	-	-
9	M	6	6	14	7	145	+	+	-	-
10	M	6	4	60	60	120	-	+	-	-
11	F	3	5	60	7	150	-	-	-	-
12	M	3	2.7	7	7	50	-	-	+	+
13	M	4	2	60	2	7	-	-	-	-
14	F	2.5	1.5	30	14	7	-	-	-	+
15	F	6	5	30	7	120	+	+	+	+
16	F	3	2	30	30	30	-	-	-	-
17	F	6	4.5	45	45	145	+	-	-	-
18	F	6	3	90	30	90	-	-	-	-
19	F	5	4	30	20	30	+	+	-	+
20	F	6	4	60	60	120	-	+	-	-
Mean ± SD		4.3 ± 1.4	3.1 ± 1.4	44.4 ± 31.8	18.8 ± 18.3	70.6 ± 48.9				

m, month(s); +, positive; -, negative

Table 2 Investigations, treatments and outcome of infants with cow milk induced gastritis

Case	Upper endoscopy	Duodenal lymphoid hyperplasia	Eosinophilic Infiltration	Ranitidine treatment	Formula	Age of cow milk tolerance (yrs)	Food allergy	Constipation	Chronic respiratory symptom	Asthma	Duration of follow-up (yrs)
1	yes	-	-	yes	EHCF soy formula	0.9	-	+	-	-	2
2	yes	+	moderate	yes nd	EHCF soy formula	1	-	-	-	-	0.8
3	nd	-	-	nd	soy formula	4	sea food	-	+	-	8
4	nd	-	-	yes	soy formula	1	-	-	-	+	1
5	yes	-	mild	yes	soy formula	1	-	-	-	-	1
6	yes	-	-	yes	soy formula	1	-	-	-	-	4
7	yes	-	mild	nd	soy formula	0.6	-	+	+	-	5
8	yes	+	moderate	nd	soy formula	2	-	-	-	+	4
9	yes	-	-	nd	soy formula	2	egg	-	-	+	4
10	yes	-	-	nd	soy formula	2	-	+	+	-	3
11	nd	-	-	nd	soy formula	0.8	-	-	-	-	3
12	yes	-	-	nd	soy formula	1	-	-	-	-	1
13	nd	-	-	nd	soy formula	1	-	-	-	+	3
14	nd	-	-	nd	soy formula	2	-	-	-	-	3
15	nd	+	moderate	nd	soy formula	3	-	-	-	-	3
16	yes	-	mild	nd	PWHF	1	-	-	-	-	1.5
17	yes	+	-	nd	PWHF	0.8	-	+	+	-	1
18	yes	+	-	nd	PWHF	1.3	-	-	-	-	1
19	yes	+	mild	nd	soy formula	2	-	-	-	-	1.5
20	yes	+	moderate	nd	PWHF	1	-	-	-	-	0.5
Mean ± SD						1.5 ± 0.9					2.6 ± 1.8

EHCF = extensively hydrolyzed casein formula; PWHF = partially whey hydrolyzed formula; yrs, years; nd, not done; +, positive; -, negative

erosion and friability of gastric mucosa in all patients and lymphoid hyperplasia in the duodenal bulb in 7 patients. All histology of the gastric mucosa showed infiltration of inflammatory cells. Four patients had mild eosinophilic infiltration (< 5 cells/high power field; HPF) and the other 4 patients had moderate eosinophilic infiltration (5-10 cells/HPF). Inflammation of the esophagus or duodenum was not demonstrated. Eosinophilia was found in 2 cases of mild eosinophilic infiltration and in 1 case of moderate eosinophilic infiltration.

Immunologic studies including total IgE, specific IgE for cow milk, or skin prick test were not performed in any case. The diagnosis of cow milk allergy in these patients was based on the clinical response after eliminating cow milk and on the histology of the gastric mucosa. Elimination and challenge test was not done due to parental refusal. Note that, the challenge test should not be done earlier than 9-12 months after the elimination.⁶

The primary treatment therapy was changing the cow milk formula to a non-allergic formula. Two patients were initially given extensively hydrolyzed casein formulas followed by a soy formula, 14 patients were given a soy formula and 4 patients were given partially whey hydrolyzed formulas. Only five patients were treated with ranitidine for 1-2 days. All patients showed improvement of symptoms a few days later. The patients' parents were advised to be re-exposed to cow milk at 1 year of age,⁷ however, some parents gave cow milk at an earlier or later date. The average age when patients were able to tolerate cow milk was

1.5 ± 0.9 years old. During the follow-up period of 2.6 ± 1.8 years following treatment, 4 of the patients were diagnosed with asthma, 4 with chronic respiratory symptoms, 4 with constipation and 2 with food allergies.

DISCUSSION

This study showed that gastritis due to CMA was more common than GERD in infants with hematemesis. There were only 3 cases of GERD which included one sick infant and 2 healthy infants. In Thai infants, chronic regurgitation or vomiting related to GERD is common, but hematemesis is rarely found. It is suggested that CMA induced gastritis is the most common cause of hematemesis in Thai infants.

In the CMA group, 15 patients (75%) had gastroduodenoscopy performed which showed only gastritis, therefore esophagitis or duodenitis were not the cause of the hematemesis. Lymphonodular hyperplasia of the duodenal mucosa has been described in association with food allergy.⁸ Endoscopic examination can be used as a means of assessing gastrointestinal food allergy. Seven cases (45%) had lymphonodular hyperplasia of the duodenal bulb similar to a previous study. Al Mouzan *et al.*³ reported a 3.5-month-old boy with hematemesis due to erosive gastritis following feeding with whole cow milk. The presence of eosinophilic infiltration of the stomach and disappearance of symptoms after discontinuing cow milk feeding suggested the diagnosis of CMA-induced hematemesis. Harikul *et al.*⁴ reported 29 Thai infants with diagnosis of CMA. Their data showed

20 cases with diarrhea, 7 cases with hematemesis and 2 cases with both diarrhea and hematemesis. Gastroduodenoscopy was not performed in cases of hematemesis, so endoscopic findings and a histology description of the gastroduodenal tract were not demonstrated.

Our patients did not have any evidence of small or large bowel involvement such as chronic diarrhea, malabsorption, edema and colitis. Lesions were localized to the stomach and the first part of the duodenum. Sampson and Anderson⁵ categorized the gastrointestinal manifestations due to immunologic reactions to foods in infants and children. Gastritis was classified in mixed IgE and non-IgE disorders as allergic eosinophilic gastritis. Its manifestations and natural history were different from that in our data. In allergic eosinophilic gastritis, the age at onset ranges from neonate to adolescent. Fifty percent of cases have atopic disease and eosinophilia. The pathology shows marked eosinophilic infiltration of the gastric mucosa and submucosa, especially in the antral part. Symptoms include post-prandial vomiting, abdominal pain, anorexia early satiety and hematemesis. Our study revealed different histories and symptoms: only one case with a family history of asthma, one case with infantile eczema, 5 cases with recurrent mild diarrhea and 11 cases with frequent respiratory tract symptoms. Eight cases had only mild to moderate eosinophilic infiltration of gastric mucosa and 25 percent of the cases had peripheral eosinophilia. Marked eosinophilic infiltration was not found. These findings suggested that CMA induced gastritis in infancy may not be classified as eosinophilic gastritis.

Ranitidine was started in cases 1, 2, 3, 4 and 6. The others did not receive ranitidine but responded very well to just changing the formulas. An H₂ blocker or antacid may have no role in the treatment of CMA-induced hematemesis. An extensively protein hydrolyzed formula is always recommended in the treatment of CMA.⁹⁻¹² Infants will tolerate extensively hydrolyzed cow milk formulas in most cases. Previous studies have shown that 17%-47% of children who are sensitive to cow milk are also sensitive to soy formulas.^{2,13-15} Soy formulas are not recommended in the dietary management of CMA.¹⁶ Businco *et al.*¹⁷ disagrees and suggests the use of soy formula in children with IgE-mediated cow milk protein allergy. At least 86% of young children with IgE-mediated cow milk allergy will tolerate soy.¹⁸ Fifty percent of infants with non-IgE-mediated reactions will react to soy¹⁹⁻²¹ and substitution with an extensively hydrolyzed formula should be considered. In 2000, the American Academy of Pediatrics has revised the recommendation for soy formula used in CMA and suggested that soy formulas can be fed to infants with IgE-associated symptoms of milk allergy, particularly after the age of 6 months.²² Because of the high price of hydrolyzed formulas, the majority of the patients in our study received soy formulas and tolerated them very well. Harikul *et al.*⁴ treated all infants with chronic diarrhea and/or hematemesis with soy formula. Eighty three percent of cases responded very well. A soy formula should be used initially in gastritis and chronic diarrhea due to CMA in developing countries. Infants with CMA have been found to react to partially hydrolyzed formula, so

it is not recommended.²³ Four patients received partially whey hydrolyzed formulas and had good clinical responses. However, the number of patients given partially whey hydrolyzed formula was low, and so it should not be used initially.

Most children lose their sensitivity to cow milk protein within the first 3 years of life.^{7,24} Businco *et al.*²⁵ showed that 15 of 40 patients were still allergic to cow milk at a median of 3 years later. Our patients were scheduled to be re-exposed to cow milk at one year of age. Some patients tried exposure at earlier or later time. However, at 1.5 ± 0.9 years of age, all patients had developed a tolerance to cow milk. Long-lasting sensitization to food during infancy has been shown to precede allergic airway disease occurring later in life.²⁶ Our long term follow-up showed that these patients still had some evidence of allergic reaction including asthma, chronic upper respiratory tract symptoms, constipation and other food allergies.

CMA induced gastritis is the most common cause of upper gastrointestinal hemorrhage in healthy infants. Elimination of cow milk and substitution with soy formula or extensively hydrolyzed formula is the proper management. With regard to classification of gastrointestinal manifestations due to immunologic reactions to foods, CMA induced gastritis may not be classified in the same group as eosinophilic gastritis.

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