Gastrointestinal Manifestations of Cow's Milk Protein Allergy During the First Year of Life

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Abstract

Background : Cow's milk protein sensitive enteropathy (CMPSE) is a common condition in the first year of life. Clinically CMPSE usually presents with symptoms like vomiting, chronic diarrhea, mucous bloody diarrhea and hematemesis. More unusual symptoms associated with CMPSE are infantile colic, gastroesophageal reflux and chronic constipation. The objective of this study was to assess the gastrointestinal manifestations and allergic march in CMPSE patients.

Method : The authors reviewed the records of 10 CMPSE patients observed by the Gastrointestinal Unit at King Chulalongkorn Memorial Hospital from 1997-2001 including patient characteristics, laboratory investigations, endoscopy and follow-up outcome.

Results : Of 10 CMPSE patients, the median age of CMPSE onset was 3.5 months. The gastrointestinal manifestations were hematemesis (n = 6), mucous bloody diarrhea (n = 3) and chronic watery diarrhea (n = 2). Exclusively breast-fed infants seemed to have more delayed onset of symptoms than those who were not. Anemia (n = 3), high serum IgE (n = 4) and positive skin prick test for cow's milk (n = 5) were found. Neither peripheral eosinophilia nor hypoalbuminemia was found. Endoscopy revealed acute and chronic gastritis. Treatment was successful by changing to soy or extensive hydrolysate formula with mean duration of cow's milk intolerance of 24 months. In 2-year follow-up, three of ten patients who had high serum IgE level developed allergic rhinitis and eczema.

Conclusion : CMPSE can be manifested in various symptoms. Exclusive breast feeding for more than 4 months can postpone the onset of CMPSE. Serum IgE or specific IgE level to cow's milk protein may identify the atopic career of CMPSE individuals.

Key word : Cow's Milk Protein Allergy, Infant, Gastrointestinal Manifestation

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Cow's milk protein allergy (CMPA) is not uncommon in infants from various ethnic groups. All commercial infant formulas are generally based on cow's milk, thus cow's milk protein is the first frequently administered foreign protein in the diets of the young infants. It is, therefore, not surprising that CMPA is the most prevalent allergy in infancy. The prevalence in infancy of CMPA is considered low, from 2 per cent to 3 per cent[1-3], and changing with age, estimated in David Hide's studies on the Isle of Wight to occur in 4.4 per cent of children aged 1 year, 1.9 per cent aged 2 years and 0.4 per cent aged 4 years[4]. According to a total of 10 studies published between 1979 and 1993, the estimated prevalence of CMPA in unselected infants given cow's milk formula, exclusively or in combination with mother's milk, varied from 2.2 to 5.9 per cent[5] However, 20 per cent of infants with an elevated risk of allergy will develop CMPA during the first 12 months if they are given the standard infant formula in very early life[6]. However, when considering the potentially numerous cases under-diagnosed since only recently being recognised as related to CMPA, one may consider that in fact CMPA occurs more frequently than is usually reported.

CMPA with gastrointestinal manifestations is called cow's milk protein sensitive enteropathy (CMPSE). Its usual manifestations are vomiting, hematemesis, chronic diarrhea, mucous bloody diarrhea, failure to thrive and anemia. Unusual manifestations have been reported in association with CMPSE including infantile colic[7,8], gastroesophageal reflux [9], esophagitis,[10] chronic constipation[11], proctocolitis[12] and enterocolitis[13]. The objective of this study was to assess gastrointestinal manifestations and allergic march in CMPSE patients.

MATERIAL AND METHOD

Patients

A retrospective cohort study of Pediatric Gastroenterology database for infants (aged 0-1 year) was observed by the outpatient or inpatient Pediatric Gastrointestinal service during the 5 year period from January 1997 to December 2001. Medical records of infants were reviewed and a follow-up plan was set. Data collected from patients includes sex, age at onset, age at presentation, clinical presentation, feeding practices, family history, laboratory investigation, endoscopy and 2 year follow-up outcome.

Diagnosis of CMPSE

Patients suspected to have CMPSE were studied in detail by performing modified Goldman challenge tests to confirm the diagnosis by the clinician criteria. Each patient was challenged with twice oral consumption of 30-60 ml. of cow's milk at 3-4 week interval. Clinical manifestation was recorded in detail after each challenge. Modified Goldman challenge test refered to the patient who developed consistent and similar symptoms as the original symptoms when they arrived at the hospital for the first time within 48 hours after the cow's milk challenge.

Definitions

Anemia	: Hb < 11 g/dl or Hct < 33 per cent according to WHO criteria.
Peripheral eosinophilia	: total eosinophil count > 600 cell/mm^3.
High serum IgE	: serum IgE > 15 IU/ml at infancy period.
Hypoalbuminemia	: serum albumin < 3.5 g/dl.

RESULTS

There were 10 cases of CMPSE during the 5-year period and all of them had positive modified Goldman challenge test. Female to male ratio was 1.5 : 1, in which 6 cases were females and 4 cases were males. The age at onset was between one week to one year and the median age at onset was 3.5 months. It was found that 6/10, 3/10 and 2/10 patients had hematemesis, mucous bloody diarrhea and chronic diarrhea, respectively. CMPSE mostly occurred in the first child (n = 5) of the family and one patient had a family atopy. Three of ten patients with exclusive breast feeding (≥ 4 months) seemed to have more delayed onset of symptoms than those who were not. (range 6-12 months *versus* 0.25-4 months of age) (Table 1)

Iron deficiency anemia, positive stool occult blood and positive skin prick test for cow's milk were found in 3/10, 6/10 and 5/10, respectively. Four of

Table 1. The characteristics of CMPSE patients.

Patients	Sex	Age (months)		Clinical presentation	Past and family history		Exclusive breast feeding (≥ 4 mo)
		at Onset	at Presentation		Child number	Family atopy	
1	M	3	3	Hematemesis and melena	1	-	-
2	M	12	12	Hematemesis	1	Y	Y
3	M	7	8	Hematemesis	1	-	-
4	M	0.25	0.25	Mucous bloody diarrhea	1	-	-
5	F	4.5	6	Mucous bloody diarrhea	3	-	Y
6	F	1.5	3	Mucous bloody diarrhea and hematemesis	1	-	Y
7	F	4	5	Hematemesis	2	-	-
8	F	4	4	Hematemesis	2	-	-
9	F	1	1	Chronic diarrhea	1	-	-
10	F	1	1	Chronic diarrhea	2	-	-

M = male, F = female, Y = yes, - = no

Table 2. Laboratory investigations in CMPSE patients.

Patients	Laboratory investigations							Endoscopic findings
	Anemia	Total eosinophils in peripheral blood (cell/mm^3)	Stool occult blood	Skin prick test for cow's milk	Skin prick test for lactalbumin	Serum IgE (IU/ml)	Serum albumin (g/dl)	
1	Y	120	P	N	N	ND	4.3	Mild erosive gastritis
2	-	400	N	P	N	90*	4.8	Hemorrhagic gastritis
3	-	180	P	P	N	ND	4.4	Hemorrhagic gastritis
4	-	250	P	N	N	295*	3.8	ND
5	-	140	P	P	N	1.4	3.9	ND
6	Y	95	N	P	N	ND	4.2	Chronic gastritis
7	-	330	N	N	N	71*	5.0	Severe gastritis and duodenitis
8	-	170	P	N	N	ND	4.1	Chronic gastritis
9	Y	280	P	N	N	ND	3.8	Chronic gastritis
10	-	240	N	P	N	100*	4.2	ND

Y = yes, - = no, P = positive, N = negative, ND = not done
* high serum IgE level (serum IgE > 15 IU/ml)

Table 3. Follow-up outcome.

Patients	Sex	Family atopy	High serum IgE	Age at onset of CMPSE (months)	Formula	Duration of cow's milk intolerance (months)	2-year follow-up outcome	Current age (year)
1	M	-	ND	3	Soy	Loss to follow-up	Loss to follow-up	7
2	M	Y	Y	12	eHF	48	Remission and developed allergic rhinitis (AR) and eczema at 2 years old	13
3	M	-	ND	7	eHF	24	Remission	3
4	M	-	Y	0.25	eHF	36	Remission and developed AR at 1.5 years old	7
5	M	-	-	4.5	eHF	12	Remission	6
6	F	-	ND	1.5	Soy	Recent Diagnosis	Recent Diagnosis	0.6
7	F	-	Y	4	eHF	24	Remission and developed AR at 3 years old	5
8	F	-	ND	4	eHF	24	Remission	3
9	F	-	ND	1	eHF	Loss to follow-up	Loss to follow-up	11
10	F	-	Y	1	eHF	Loss to follow-up	Loss to follow-up	3

M = male, F = female; Y = yes; - = no, ND = not done, eHF = extensive hydrolysate formula

Fig 1. Endoscopy demonstrating hemorrhagic gastritis.

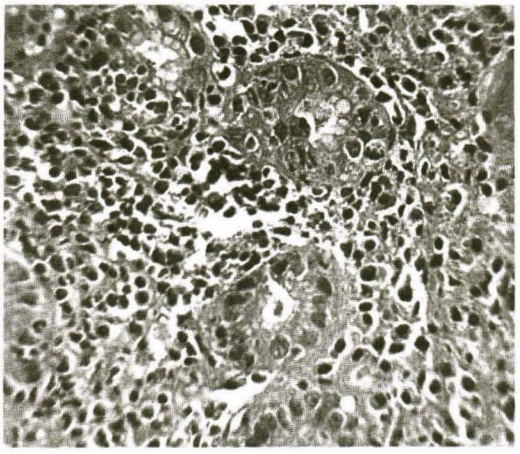

Fig. 2 Gastric biopsy specimen showing polymorphonuclear cell and eosinophilic infiltration of lamina propia and crypts. Scattered hemorrhagic foci are noted. (Hematoxylin-eosin stain, original magnification x 400)

ten patients had high serum IgE level. None had eosinophilia, positive skin prick test for lactalbumin and hypoalbuminemia. Endoscopy revealed a variety of gastritis eg. mild erosive gastritis, hemorrhagic gastritis (Fig. 1, 2) and chronic gastritis. One patient had severe gastritis and duodenitis. (Table 2)

Having confirmed the diagnosis of CMPSE, suitable milk formulations, soy or extensive hydrolysate formula (eHF) were prescribed to avoid the patient's respective allergens. Two of ten patients received soy formula according to the economic status and the remaining patients received eHF. All cases recovered thereafter with a mean duration of cow's milk intolerance of 24 months. Three of ten patients were lost to follow-up. In the 2 year outcome follow-up, the remaining patients were still in remission from CMPSE but 3 patients had subsequently developed allergic diseases such as allergic rhinitis and eczema. All of them had high serum IgE levels when reaching the first diagnosis of CMPSE. (Table 3)

DISCUSSION

It was found in the present study of that a higher prevalence of CMPSE occurred more in females than male with the ratio of 1.5:1. Mean age of 3.5 months CMPSE onset was similar to those reported in the series of Gerrard[14] which were at the age of 2-3 months. CMPSE mostly occurred in the first child and some had allergic evidence among family members. It is known that the family history of atopy and/or food allergies is one of the most important risk factors for CMPA in infancy[15]. Jacobson and Lindberg found that 35 per cent of their patients had allergic evidence among family members[16].

The infants who received exclusive breast feeding seemed to have more delayed onset of symptoms than those receiving non exclusive breast feeding (mean 6 months in exclusive breast-fed infants *versus* 3.2 months in non exclusive breast-fed infants). However, some exclusive breast fed infants might develop CMPA because they reacted against food proteins transferred from the mothers' diet into her breast milk[17].

Hematemesis was found to be the first major presenting symptom (n = 6). Since mothers of patients with hematemesis sought medical help shortly after the infants developed the illness and early diagnosis was made by experienced clinicians, anemia was less pronounced (n = 2) in the present study. Iron deficiency anemia resulted from chronic blood loss due to chronic gastritis in CMPSE patients.

Treatment of most CMPSE patients was successful by changing to soy or eHF. All patients tolerated the formula and were in remission. Three cases subsequently developed other allergic diseases. The prognosis for CMPA is generally regarded as very good, with a remission rate of over 80 per cent

up to the age of 3 years[18]. However, the remission rate was clearly lower in a recent prospective study conducted by Bishop et al[19]. Of 97 infants in whom CMPA was proven by challenge in the first postnatal year, less than 50 per cent were tolerant upon challenge at 2 years, 60 per cent at 4 years, and 80 per cent at 6 years. They also found that 75 per cent, 21 per cent and 40 per cent of patients developed an allergy to other food, atopic dermatitis and bronchial asthma, respectively. An infant with food allergy either CMPA or eczema at diagnosis, may have a chance to subsequently develop other allergic diseases especially respiratory allergies later in life. This is the so called "atopic career". The study of the typical natural history of atopic diseases in infancy found in the prospective study of Saarinen and Kajosaari who followed the infants for 17 years[20] revealed CMPA and atopic dermatitis dominated in infancy. CMPA should be concomitantly evaluated for relevance in young children with atopic dermatitis. Recent studies by Kissling and Wuthrich[21] have shown that 30-80 per cent of all children with atopic dermatitis subsequently developed a respiratory allergy.

All three from ten patients who subsequently developed allergic diseases in the present study had high serum IgE level at the first diagnosis of CMPSE. In Host's study[18], he found that infants with high IgE levels to cow's milk protein have an especially high risk of persisting cow's milk allergy, development of allergy to other foods, especially eggs and development of inhalant allergies.

In summary, CMPA is, thus, not an isolated phenomenon, but often the start of an "atopic career". Exclusive breast feeding for more than 4 months can postpone the onset of CMPSE. Serum IgE or specific IgE level to cow's milk protein may identify the atopic career of CMPSE individuals.

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อาการและอาการแสดงทางระบบทางเดินอาหารของภาวะแพ้โปรตีนในนมวัวในเด็กช่วงอายุขวบปีแรก

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ความเป็นมา : อาการทางระบบทางเดินอาหารจากภาวะแพ้โปรตีนในนมวัว พบได้บ่อยในเด็กช่วงอายุขวบปีแรก อาการที่พบบ่อยได้แก่ อาเจียน, อุจจาระร่วงเรื้อรัง, อุจจาระมีมูกเลือดปนและอาเจียนเป็นเลือด ส่วนอาการที่พบไม่บ่อยได้แก่ อาการปวดท้องโคลิก ภาวะกรดในกระเพาะอาหารไหลย้อนเข้าสู่หลอดอาหารและภาวะท้องผูกเรื้อรัง การศึกษานี้มีจุดประสงค์เพื่อศึกษาอาการและอาการแสดงของระบบทางเดินอาหารและภาวะโรคภูมิแพ้ระบบอื่น ๆ ที่อาจพบได้ในผู้ป่วยทารกที่แพ้โปรตีนในนมวัว

วิธีการศึกษา : เป็นการศึกษาย้อนหลังในผู้ป่วยเด็กที่แพ้โปรตีนในนมวัว จำนวน 10 รายที่มารักษาที่หน่วยทางเดินอาหาร โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่พ.ศ. 2540 ถึง 2544 โดยศึกษาในด้านอาการและอาการแสดงทางคลินิก การตรวจทางห้องปฏิบัติการ การส่องกล้องทางเดินอาหารและการติดตามผลการรักษาระยะยาว

ผลการศึกษา : จากเด็กที่ศึกษาจำนวน 10 ราย พบว่าอายุเฉลี่ยที่เริ่มมีอาการเท่ากับ 3.5 เดือน อาการที่พบได้แก่ อาเจียนเป็นเลือด 6 ราย ถ่ายเป็นมูกเลือด 3 ราย และอุจจาระร่วงเรื้อรัง 2 ราย ตามลำดับ และพบว่าเด็กที่ได้รับนมมารดาอย่างเดียวเป็นเวลาอย่างน้อย 4 เดือน จะมีอาการของภาวะนี้ช้ากว่าเด็กที่ได้รับนมมารดาน้อยกว่า 4 เดือน ส่วนอาการแสดงพบภาวะซีด 3 ราย ภาวะอิมมูโนโกลบูลินอีสูงในซีรั่ม 4 ราย และจากการทดสอบทางผิวหนังพบผลบวกต่อโปรตีนในนมวัว 5 ราย ไม่พบว่ามีอีโอสิโนฟิลสูงและอัลบูมินต่ำในเลือด จากการส่องกล้องทางเดินอาหารพบว่า มีการอักเสบเฉียบพลันและเรื้อรังของกระเพาะอาหาร ผู้ป่วยได้รับการรักษาโดยเปลี่ยนจากนมวัวเป็นนมถั่วเหลืองหรือนมโปรตีนไฮโดรไลเสทฟอร์มูล่า ระยะเวลาเฉลี่ยที่อาการแพ้หายไปเท่ากับ 24 เดือน หลังจากติดตามผลการรักษา 2 ปี พบว่าเด็ก 3 คนที่มีอิมมูโนโกลบูลินอีสูงในซีรั่มมีอาการภูมิแพ้ทางจมูกและมีผื่นแพ้ผิวหนังเกิดขึ้น

สรุป : การให้นมมารดาอย่างเดียวเป็นเวลาอย่างน้อย 4 เดือน สามารถเลื่อนระยะเวลาที่ก่อให้เกิดอาการแพ้โปรตีนในนมวัวให้นานออกไป ซีรั่มอิมมูโนโกลบูลินอีหรืออิมมูโนโกลบูลินที่จำเพาะต่อโปรตีนในนมวัว อาจจะคาดเดาถึงภาวะภูมิแพ้ทางระบบอื่น ๆ ที่ผู้ป่วยอาจจะเป็นในอนาคต

คำสำคัญ : ภาวะแพ้โปรตีนในนมวัว, ทารก, อาการและอาการแสดงทางระบบทางเดินอาหาร

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