ORIGINAL ARTICLE

Cow's Milk Protein-Sensitive Enteropathy (CMPSE) in Infant With Chronic Diarrhea

by

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Abstracts

Six cases of CMPSE as revealed by biopsy studies and clinical symptoms are presented. All infants suffered from chronic diarrhea, of which 5 developed failure to thrive.

No pathogenic microorganism was isolated from the stools. Stool ova and parasites were also negative. Lactose intolerance was not found among these infants. The possible pathogenesis has been briefly discussed. The present series obviously indicates that CMPSE does occur in Indonesia.

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Introduction

The growing use of cow's milk in the last few decades, the interest aroused by immunologic responses to ingested proteins, and the discovery of several syndromes due to cow's milk allergy have become arising problems. Estimates of the incidence of cow's milk allergy vary from 0.1 to 8 percent of the population (Bahna, 1978; Eastham et al., 1978; Freier and Kletter, 1970; Walker Smith et al., 1978). High antibody levels are seen in infants in whom cow's milk is introduced during the first month of life (Bahna, 1978; Iyngkaran et al., 1978; Powell, 1978; Walker Smith, 1978). 67% of the milk allergic children were bottle fed from the first day of life (Buisseret, 1978).

Gastrointestinal allergy to cow's milk is usually characterized by chronic diarrhea with passage of mucus and watery stools with or without gross or occult blood. Some children may pass the typical fatty stools of steatorrhea (Walker Smith, 1978).Most children have their symptoms within the first six months of life (Walker Smith, 1978). CMPSE is recognised as a significant cause of chronic infantile diarrhea and failure to thrive in babies and until now the diagnosis is still difficult (Harrison et al., 1976; Iyngkaran et al., 1978; Iyngkaran et al., 1979; Suharyono, 1980).

Iyngkaran et al. (1979) have found that 21 infants out of 26 with protracted diarrhea, had CMPSE. In the past, diagnoses were based on certain clinical criteria described by Goldman et al. (1963). The Goldman's criteria are sound but frequently not practical, as many mothers refuse to accept the frequent milk challenges required, it may also be extremely dangerous in very sensitive patients. (Easthman and Walker, 1977; Iyngkaran et al., 1978; Hock and Boon, 1980; Walker Smith et al., 1978). Recently, Shiner et al. (1975), Iyngkaran et al. (1978) and Walker Smith et al. (1978), applied a combined clinical and histological approach to the diagnosis CMPSE.

The purpose of this paper is to present 6 cases of CMPSE in infants with chronic diarrhea.

Abbreviations used :

CMP = Cow's milk protein

CMPSE = Cow's milk protein sensitive enteropathy.

Material and methods

The series consisted of 6 infants with CMPSE seen between December 1979 and March 1980 who fulfilled the diagnostic criteria as shown in Table 1.

All the patients were admitted to the Paediatric ward of the Dr. Soetomo Hospital, Surabaya.

Initial intestinal biopsy (first biopsy) was performed as soon as the infant was rehydrated. If the biopsy was abnormal the infant was fed a diet free of CMP for 3 - 4 weeks, such as breast milk, Progesimil or, if not available, Prosobee. A second (Pre-challenge) biopsy was performed after 3 - 4 weeks on CMP free diet as preliminary to a Cow's milk challenge.

After each infant had a second biopsy which showed a normal or near to normal small bowel mucosa, they were given a lactose challenge followed by cow's milk challenge. The third (post challenge) biopsy was performed 48 - 72 hours after the challenge with cow's milk.

TABLE 1: *Criteria for the diagnosis of CMPSE*

1. a. History of diarrhea for 2 or more weeks.
   b. Aged between 2 months and 1 year.
   c. Partially or wholly fed cow's milk or a cow's milk formula.
   d. Presence of abnormal small intestinal mucosa on biopsy.
2. Symptoms subside after dietary elimination of cow's milk, with normal or near to normal intestinal mucosa.
3. Reappearance of an abnormal small intestinal mucosa on biopsy 48 - 72 hours after challenge with cow's milk.

Results

The clinical syndrome of CMPSE was found more often in boys than in girls (Table 2). Most of them were Javanese of origin (Table 3).

Two infants out of 6 had received cow's milk since birth. All of them were fulterm, delivered with birth weights ranging from 2600 grams to 3750 grams. The age on admission and duration of illness are shown in Table 4.

All infants had symptoms of diarrhea for 2 weeks or more before admission. Five infants out of 6 showed some degree of failure to thrive (Table 5).

The clinical features on admission are summarized in Table 6. Only half of the number of patients had a history of vomiting in addition to the diarrhea and clinical evidence of dehydration was also seen in half of the patients on admission. One infant had a history of atopic rhinitis.

All 6 infants tolerated Progestimil. On challenge with cow's milk formula 3 - 4 weeks later, 3 of them developed transient diarrhea (Table 7).

Clinitest showed negative results, and the diarrhea subsided spontaneously within 24 hours. However, on follow-up, all 6 infants subsequently turned to be intolerant to cow's milk 1 - 2 weeks after the milk challenge, necessitating to put them back on Progestimil or meat based diets.

A second small bowel biopsy taken 3 - 4 weeks after cow's milk free diet showed either normal or mildly abnormal pictures of the mucosa. Subsequent biopsies taken 48 hours after the reintroduction of a cow's milk formula showed increased mucosal damage in all 6 infants. (Table 8).

TABLE 2: *Sex ratio in this series as compared to the series of Hock and Boon (1980)*

Sex ratio	Present series (N = 6)	Hock and Boon (N = 19)
M/F	4/2	10/9

TABLE 3: *Racial distribution*

Race (N = 6)	Number	Percentage
Javanese	3	50
Madurese	2	33.3
Chinese	1	16.7

TABLE 4: *Age on admission and duration of illness of 6 patients as compared with the material of Hock and Boon (1980)*

		Present series	Hock and Boon
Age on admission	Mean	7.4 months	8.1 weeks
	Range	2 — 10 months	2 — 34 weeks
Duration of symptoms before admission	Mean	33 days	3.8 weeks
	Range	15 — 75 days	3 days — 14 weeks

TABLE 5: *Weight on admission*

50 per-centile Standard Harvard	Number of patients	Percentage
80 — 90%	1	16.7
70 — 80%	2	33.3
60 — 70%	2	33.3
60%	1	16.7

TABLE 6: *Clinical features*

	No. of pat.	Present series %	Hock and Boon %
Diarrhea	6	100	100
Vomiting	3	50	37
Dehydration	3	50	26
Persistent rhinitis	1	16.7	—
Stools culture negative	6	100	100
Stools parasites negative	6	100	—

TABLE 7: *Course of disease as influenced by intake of cow's milk of Hock and Boon's series*

	No. of pat.	Present series %	Hock and Boon %
1. Symptoms subsided after dietary elimination of cow's milk.	6	100	100
2. Symptoms recurred within 48 hours after challenge wth cow's milk.	3	50	75

TABLE 8: *Biopsy data of the 6 infants (Classification based on dissecting microscope appearances).*

No.	Case	Initial biopsy	Pre-challenge biopsy	Post-challenge biopsy
1.	S	Flat mucosa	Broad villi	Thickened ridges
2.	SBU	Thickened ridges	Broad villi	Thickened ridges
3.	IS	Thickened ridges	Broad villi Patchy lesions	Flat mucosa
4.	RN	Thickened ridges	Broad villi Patchy lesions	Flat mucosa
5.	N	Thickened ridges	Broad villi	Flat mucosa
6.	K	Thickened ridges	Patchy lessions	Thickened ridges

Discussion

In our series 2 out of 6 infants had received cow's milk since birth and the ages on admission varied from 2 to 10 months. According to Anderson and Burke (1975), diarrhea is considered to be the usual presenting symptom in infants fed on cow's milk from birth, and it may be mild or severe enough to require prolonged intravenous therapy.

Factors such as increased intestinal permeability to milk protein during the newborn period may contribute to the susceptibility of young infants to milk sensitivity (Eastham and Walker, 1977; Freier and Kletter, 1970; Gryboski, 1967). Besides, a small infant who contracts acute infective enteritis (AIE) suffers damage and increased permeability of the gut mucosa by the aetiological agent. Gut permeability to cow's prote-

in antigen may result in sensitization, so that a subsequent challenge with cow's milk protein may cause an immunological reaction on the gut wall resulting in additional mucosal damage, malabsorption, secondary sugar intolerance, continuing diarrhea and failure to thrive (Bahna, 1978; Buisseret, 1978; Iyngkaran et al., 1978).

Allergy to cow's milk is more common in atopic infants and their families than in the normal population (Bahna, 1978; Schwachman, 1973; Walker Smith, 1978). In the present series, however, none had a family history of allergic disease, and only one had persistent rhinitis. Freier and Kletter (1970) found that 70% of infants with cow's milk allergy had a family history of allergic disease.

A pre- anl post-challenge biopsy is essential for accurate interpretation of post-challenge appearances, because of variable severity. The severity of this mucosal abnormality, however, varies from child to child and from series to series. Despite biopsy changes in all infants, diarrhea developed only 1 to 2 weeks after the challenge. Recent evidence also suggested that milk challenge might not cause any clinical symptoms for as long as three to four weeks. (Eastham et al., 1978).

According to Iyngkaran et al., (1978) an important implication for management is as follows :

1. In infants with post-challenge biopsy changes and symptoms cow's milk protein (CMP) should be excluded from the diet.
2. Infants with biopsy changes without symptoms may be managed with a cow's milk formula but will need careful follow-up and the exclusion of CMP should gastrointestinal or other allergic symptoms appear within a reasonable time after provocation i.e. before 3 months.

The use of preliminary lactose challenge enables continuing lactose intolerance to be excluded as a cause of milk intolerance before proceding to a milk challenge.

Harrison et al., (1976) suggested a possible association between CMPSE, lactose intolerance and acute infective enteritis (AIE). In infants with AIE feeding of CMP during recovery caused damage to the small bowel mucosa.

The damage itself could perpetuate to the diarrhea or, by depletion of the mucosal disaccharidases, produce symptoms due to secondary sugar intolerance (Eastham and Walker, 1977; Harrison et al., 1976).

The severity and extent of damage, the amount of lactose, the amount and type of CMP in the diet, the ability of the infants to digest the protein and render it harmless, their ability to mount an appropriate immunological reaction, and the presence of intercurrent enteric infections are some factors that may determine whether or not symptoms manifest in them. (Harrison et al, 1976; Iyngkaran et al., 1978). How;ever

secondary sugar intolerance can be a complication of any enteropathy including CMPSE so that exclusion of CMP as well as lactose from the diet is essential in the nutritional rehabilitation of these infants (Iyngkaran et al, 1979; Schwachman et al., 1973; Hock and Boon, 1980).

Total elimination of cow's milk and dairy products is required when infants with post-challenge biopsy changes produce symptoms. The formulas that are available and contain hydrolysed protein (Nutramigen, Progestimil), may be used, as well as meat protein or soy protein supplemented with needed vitamins and minerals, if breast milk is not available (Anderson et al., 1975; Freier et al., 1969; Gryboski 1975; Iyngkaran et al., 1978).

Challenge with small amounts of CMP may be undertaken once every two to three months until the allergy disappears (Lebenthal, 1975). Hock and Boon (1980) used rice water in the management of malignant diarrhea and cow²s milk intolerance with highly satisfying results. The concentration of rice water is increased gradually, the child is fed with a spoon and at this stage, boiled fish, mincemeat, egg and other solids can be introduced gradually.

The chief advantages of using breast milk in the management of CMPSE are known :

1. Breast milk has a distinctive value in diagnosis. A good response with breast milk can only be due to cow's milk intolerance, as human milk also contains lactose (Hock and Boon, 1980).
2. It is a therapeutic value at the same time (Suharyono, 1980; Hock and Boon, 1980).
3. It prevents the occurrence of CMPSE especially when given since birth (Bahna, 1978; Buisseret, 1978; Freier and Kletter, 1970).

If breast milk is not available a hypoallergenic formula i.e. Progestimil, Prosobee could be given during the period before local immunity is established (first six weeks of life) (Eastham et al., 1978; Freier et al., 1969).

The original evidence that soy bean protein is "hypoallergenic" is now in question, with numerous recent reports of adverse reactions (including villous atrophy) in infants and older children (Eastham and Walker, 1977).

Freier et al. (1969), Iyngkaran et al. (1979), Hock and Boon (1980), found that a large proportion of the babies with cow's milk intolerance also showed intolerance to soy bean protein.

Many of the patients developed intolerance to other food proteins, such as soy bean protein, gluten, if these were given during the sensitive period.

Soy protein allergy together with milk protein allergy has been described (Hock and Boon, 1980).

Milk allergy usually disappears spontaneously, within one to two years presumbly due to the maturation of the in-

testinal tract (Anderson and Burke, 1975; Bahma, 1978; Freier et al., 1969). By the end of the first year of life 17% to 85% of milk sensitive infants were able to tolerate one form of milk or another (Bahna, 1978). However, the later development of other allergics occurs in the majority of patients. The rhinorr hoea, nasal stuffiness, eczema and diarrhea in infancy may be replaced by abdominal pain, headache, or asthma in later childhood and into adult life (Bahna, 1978). Thus milk allergy may still be present but unrecognised because the manifestations have changed with the passage of time.

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