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Malabsorption syndrome with cow's milk intolerance

Clinical findings and course in 54 cases

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Kuitunen, P., Visakorpi, J. K., Savilahti, E., and Pelkonen, P. (1975). *Archives of Disease in Childhood*, **50**, 351. **Malabsorption syndrome with cow's milk intolerance: clinical findings and course in 54 cases.** Fifty-four infants with the malabsorption syndrome and cow's milk intolerance seen during 1962–1971 were investigated. All had diarrhoea and failed to thrive. Most had vomiting and about 20% had atopic eczema and recurrent respiratory infections. Laboratory investigations revealed malabsorption, raised serum IgA, and precipitins to cow's milk. Biopsies showed that the jejunal mucosa was damaged, and in about half the cases was flat. The patients did well on human milk but reacted clinically to cow's milk challenge, either in a few hours or gradually during 3–4 weeks. Some patients showed first a quick, but later a slow, reaction. Clinical symptoms of cow's milk intolerance disappeared at the age of about one year. At that time 81% had normal faecal fat, but only 29% had a normal proximal jejunal mucosa. Many of the patients developed intolerances to other food proteins, such as soya and wheat, if these were given during the sensitive period. Forty-two patients have been followed up for 2 years on a normal gluten-containing diet. Of these, 37 have a normal or nearly normal jejunal mucosa and 5 (12%) have subtotal villous atrophy indicative of coeliac disease.

It is concluded that the malabsorption syndrome with cow's milk intolerance is a clear-cut clinical entity. However, the symptomatology, results of laboratory tests, and jejunal biopsy findings closely resemble those of other entities where damage to the intestinal mucosa causes a malabsorption syndrome. Follow-up studies showed that the disease is transient, but about 10% of the patients have coeliac disease, regarded in such cases as the primary disorder.

Cow's milk allergy or 'illness induced by cow's milk' leads to a variety of clinical symptoms, respiratory, cutaneous, or gastrointestinal (Gerrard *et al.*, 1973; Gryboski, 1967; Freier, 1973). During the past decade we have studied the condition in which chronic diarrhoea and the malabsorption syndrome with jejunal mucosal changes are apparently caused by cow's milk proteins (Kuitunen, Visakorpi, and Hallman, 1965; Kuitunen, 1966; Kuitunen *et al.*, 1973). Particular attention was paid to the clinical course of the disease and to the late prognosis.

Material and methods

Patients. The series consisted of 54 consecutive patients with this syndrome seen at the Children's Hospital, University of Helsinki, during 1962–1971 (Table I), who fulfilled the following diagnostic criteria. (1) Prolonged gastrointestinal symptoms and malabsorption verified by absorption tests (faecal fat >3 g/d and/or urinary D-xylose excretion <15%). (2) Disappearance of symptoms after elimination of cow's milk. (3) Reaction to cow's milk challenge with gastrointestinal symptoms and/or poor weight gain. 27 children had never eaten gluten; 27 had done so, 11 not until the onset of gastrointestinal symptoms and 16 before onset.

Elimination and provocation. Treatment was started by eliminating cow's milk, and feeding human milk. Clear clinical improvement resulted, usually in a few days. In some patients, however, the diarrhoea continued, apparently due to secondary lactose malabsorption. Some even had to be given parenteral nutrition initially, followed by gradually increasing feeds of human milk. When the clinical condition was

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TABLE I

Details of 54 patients with malabsorption syndrome and cow's milk intolerance

No. of patients	Boys/ girls	Mean age at onset of symptoms (range)	Mean duration of cow's milk feeding before onset of symptoms (range)	Mean age on admission (range)
54	25/29	9w (1d–22w)	4w (1d–18w)	15w (4d–44w)

satisfactory, a provocation test was made with an unadapted cow's milk formula (100 ml contains 2·2 g protein, 2·2 g fat, 0·26 g sucrose, and 7·28 g lactose) made from powdered cow's milk. Starting with a single oral dose of 5 ml, if no clinical reaction was observed, 10 ml was given with every meal and the dose was then gradually increased daily. Within a week the child was put on cow's milk formula alone if there was no reaction. If gastrointestinal symptoms (vomiting and/or diarrhoea) occurred within one day the reaction was called *rapid*. If the reaction set in later on, it was called *slow*. If no reaction was observed within 4 weeks, the result of the challenge was considered to be negative. In addition, 8 patients were tested with isolated cow's milk protein fractions and 19 with wheat (Tables V and VI) when still intolerant to cow's milk. Other food intolerances were observed when these foods were introduced into the diet. After 2–4 months human milk was replaced by soya milk or Nutramigen and the child was sent home on this diet. This elimination diet was also gluten-free. The patients were readmitted at the age of 6–14 months to test whether they could now tolerate cow's milk. Cow's milk elimination was discontinued as soon as possible. Gluten-containing food was allowed, usually about 5–6 months after cow's milk had been reintroduced, without preliminary testing, but usually not before the intestinal mucosa was clearly improved. Follow-up examinations were done when the child had been on a normal diet for 1 and 2 years.

Methods. Faecal fat was measured by the method of van de Kamer *et al.* (1949) in a 3-day sample. The D-xylose excretion test was performed with a 5-hour sample of urine after the ingestion of 350 mg D-xylose/kg body weight. Urinary FIGLU was measured by high-voltage electrophoresis (Knowles, 1962) from 12-hour urine after a single L-histidine load (350 mg/kg). Urinary and faecal sugars were measured by thin-layer chromatography. In some patients, in addition, the stools were studied by the Clinitest method. Immunological tests were performed as described by Immonen (1967). Other laboratory tests were performed by routine methods. The proximal jejunal biopsy specimen was taken with the Crosby-Kugler capsule of paediatric size near the ligamentum of Treitz and examined under a dissecting microscope (Booth *et al.*, 1963) and by light microscopy (Kuitunen, 1966).

Results

Symptoms and signs (Tables I and II). The malabsorption syndrome with cow's milk intolerance is a disease of early infancy. The gastrointestinal symptoms appear on average at 2 months, and after about 1 month's cow's milk feeding. Vomiting is often accompanied by prolonged diarrhoea and failure to gain weight. 14 infants (26%) were severely dehydrated on admission and required intravenous fluids. 3 of these were fed parenterally for 40 days, 4 months, and 7½ months, respectively. On admission 4 infants were suspected to have ileus and 2 even underwent laparotomy. Recurrent respiratory infections and eczema were common. 4 infants had Down's syndrome.

Initial laboratory and biopsy findings. Absorption tests indicated malabsorption, this being a condition for the diagnosis (Table III). Lactose absorption was not studied systematically but lactosuria was found in 18 out of 33 patients and

TABLE II

Symptoms and signs in 54 patients with malabsorption syndrome and cow's milk intolerance

Diarrhoea	Vomiting	Macroscopical blood in stools	Severely dehydrated on admission	Mean weight on admission* (−SD)	Eczema	Recurrent respiratory infections	Down's syndrome
54/54	36/54	6/54	14/54	−3·3 (−1·1– −5·85)	12/54	13/54	4/54

*Standard deviation calculated from the normal weight tables of Finnish children.

TABLE III

Initial laboratory and biopsy findings in 54 patients with malabsorption syndrome and cow's milk intolerance

Laboratory findings	
Faecal fat excretion >3 g/d	42/51
D-xylose excretion <15%	38/53
Positive urinary FIGLU test	40/50
Haemoglobin <10 g/dl	11/53
Eosinophils in blood >4%	17/52
Serum alkaline phosphatase activity >10 B–L units	5/49
Prothrombin <80%	26/52
Serum total protein <5·5 g/100 ml	14/45
Increased serum IgA (= > +2SD)	37/50
Precipitins to cow's milk	32/49
Precipitins to gluten	6/49
Generalized aminoaciduria	10/24
Stool culture:	
Staphylococcus aureus	15/53
Staphylococcus albus	1/53
Pseudomonas aeruginosa	3/53
Enteropathogenic *Esch. coli*	1/53
Proximal jejunal biopsy findings	
Normal villous structure (finger- and leaf-shaped villi)	1/48
Slight villous changes (high ridges)	3/48
Partial villous atrophy (convoluted mucosa)	17/48
Subtotal villous atrophy (flat mucosa)	27/48

increased amounts of lactose in the stools in 12 out of 23 patients. In addition, Clinitest was clearly positive in 4 out of 7 patients. All these tests indicated lactose malabsorption in about half the patients. Immunological studies showed increased serum IgA content and precipitins to cow's milk, but precipitins to gluten were rare. In most infants no pathogenic organisms were found. The pathogenic roles of *Staph. aureus* and *albus* are not clear. Tests for *Giardia lamblia* were not systematically carried out. Jejunal biopsy often revealed severe mucosal damage of the type seen in coeliac disease. In one infant villous structure was normal, but the villous epithelium had a slight intraepithelial round-cell infiltration, and the nuclei were somewhat disorientated.

Reactions to provocation. In 28 infants the first reaction to cow's milk was rapid and in 26 it was slow. In some patients an initial rapid and later a slow reaction were discernible. This may explain why the mean age of the patients who reacted rapidly was lower (Table IV). Reactions to some cow's milk protein fractions are summarized in Table V. Positive reactions were most frequent with β-lactoglobulin and casein. Reactions to some other foods can be seen in Table VI. In addition, 2 patients reacted to bananas, 2 to eggs, and one to beef. All the challenges were performed when the patients were still intolerant to cow's milk. Thus these patients readily develop sensitivities to other foods besides cow's milk, if exposed to them early.

Recovery from cow's milk intolerance. Because challenges could not be repeated systematically, it was impossible to determine the exact age at which clinical cow's milk intolerance disappeared. The age at the latest positive challenge, and the point at which the patients no longer reacted to cow's milk, suggest that tolerance develops between about 31 and 58 weeks (Table IV).

Recovery from the disease. The results of investigations made at the time of reintroduction of cow's milk and reintroduction of gluten into the diet showed that gradual improvement occurred (Table VII). In most patients malabsorption could no longer be detected at ages of 1–1½ years, but the proximal jejunal mucosa was often still abnormal. The histological structure of the surface epithelium improved considerably within a month on breast milk.

Late prognosis. Results of follow-up biopsies of the proximal jejunal mucosa are presented in Table VIII. We were able to re-examine 42 patients who had been on a gluten-containing diet for 2 years or more. In 33 of these the proximal

TABLE IV

Challenges with cow's milk in 54 patients with malabsorption syndrome and cow's milk intolerance

Mean age (and range) at time of first challenge		Mean age (and range) at time of latest positive challenge	Mean age (and range) at time when patients no longer reacted to challenge
Rapid reaction (28 patients)	Slow reaction (26 patients)		
16w (8w–52w)	26w (11w–53w)	29w (13w–73w)	55w (22w–108w)

TABLE V

Reactions to some cow's milk protein fractions in 8 patients with malabsorption syndrome and cow's milk intolerance

Case no.	Proteins used in provocations*				
	Casein (2800 mg)	Lact-albumin (100 mg)	β-lacto-globulin (320 mg)	Bovine serum albumin (40 mg)	Bovine γ-globulin (80 mg)
1†	+	−	+	−	−
2†	+	−	−	−	−
3†			+	−	
4†	+		+	+	−
5					+
6	+	−	+	−	−
7	−	+	+	−	
8	+		+	−	
	5/6	1/4	6/7	1/7	1/5

*Casein obtained from Hoffman-La Roche; lactalbumin and β-lactoglobulin from Nutritional Biochemicals Co.; bovine albumin powder and bovine γ-globulin from Armour Pharmaceutical Company Ltd. The doses correspond roughly to the content of protein in 100 g whole milk.

†Data concerning these patients have been published (Visakorpi and Immonen, 1967).

TABLE VI

Clinical intolerance to soya, wheat, and Nutramigen in patients with the malabsorption syndrome and cow's milk intolerance

Soya	Wheat	Nutramigen
4/35	7/19	3/17

jejunal mucosa was completely normal; 4 had slight mucosal changes in the surface epithelium of the villi, but the villous structure looked normal both under the dissecting microscope and on histological section. 5 patients had subtotal villous atrophy (flat mucosa) of the type seen in untreated coeliac disease. Those 7 patients who were followed up for less than 2 years on a gluten-containing

TABLE VIII

Proximal jejunal biopsy findings at follow-up for more than 2 years in 42 patients with the malabsorption syndrome and cow's milk intolerance*

Appearance of proximal jejunal mucosa	
Normal	33
Slight mucosal changes	4
Subtotal villous atrophy	5
Total	42

* Of the whole 1962–1971 series of 54 patients, 7 were followed for less than 2 years, and 5 were not followed up.

TABLE VII

Laboratory and biopsy findings at the time of reintroduction of cow's milk and gluten into the diet

	Results at time of reintroduction of cow's milk	Results at time of reintroduction of gluten
Age of patients		
(mean)	55w	78w
(range)	23w–114w	29w–261w
Faecal fat excretion >4 g/d	4/41	2/29
D-xylose excretion <15%	11/41	4/32
Positive urinary FIGLU test	9/33	5/7
Increased serum IgA (> +2SD)	4/42	3/36
Precipitins to cow's milk	16/37	26/37
Precipitins to gluten	0/37	0/37
Normal proximal jejunal mucosa	10/35	18/35
Abnormal proximal jejunal mucosa	25/35	17/35
Slight mucosal changes	8/35	8/35
Partial villous atrophy	14/35	6/35
Subtotal villous atrophy	3/35	3/35

diet had a completely normal proximal jejunal mucosa.

Comparing the 5 patients who had a flat mucosa with the others the following points emerged. Their average age at onset of symptoms and the average age on admission were higher. At the initial biopsy the proximal jejunal mucosa was flat in each of the 5, and recovery was slow. In 2 patients full normalization of the proximal jejunal mucosa on the gluten-free diet took 2 years and 4½ years, and in 2 other patients only partial recovery was attained in 2½ years and 5 years, respectively. In the fifth patient normalization of the proximal jejunal mucosa did not occur because she did not keep to the gluten-free diet prescribed.

Provocation with gluten in the 4 patients with completely or partially normalized mucosa resulted in clear deterioration of the structure of the proximal jejunal mucosa. So we consider that at least these 4, and presumably also the fifth patient with a persistently flat mucosa, suffer from coeliac disease.

Discussion

This report summarizes the clinical data collected by us during the past 10 years in connexion with our study of the malabsorption syndrome with cow's milk intolerance. Our findings concerning the clinical picture of the disease and the initial laboratory findings are fairly consistent with the data presented in many other papers (Fällström, Winberg, and Andersen, 1965; Lamy *et al.*, 1963; Liu *et al.*, 1968). The onset of this disease seems to be limited to early infancy, and thus may lead to severe dehydration and a dangerous situation, sometimes necessitating parenteral nutrition.

Classic allergic phenomena like eczema and eosinophilia are often associated with this disease. Laboratory tests in general give results similar to those found in other malabsorptive diseases, so that even with jejunal biopsy these tests fail to provide criteria for differentiating this disease, and clinical challenge becomes crucial for diagnosis. A rapid, even anaphylactic, reaction is the typical response to challenge with cow's milk, but a different and slower response is also quite common, anorexia, bulky stools, and poor weight gain appearing within 3–4 weeks. This 'slow' reaction closely resembles that seen in coeliac disease after challenge with gluten. In the initial stages of the disease, when the process is very active, the reaction to challenge is rapid, but later becomes slower. Finally, asymptomatic reactions may occur, as suggested by Savilahti (1973).

A significant observation is that these patients tend to develop sensitivities to other food proteins in addition to cow's milk protein. As challenges with milk protein fractions have shown, intolerance to cow's milk is based on a complex sensitivity to many fractions, though β-lactoglobulin seemed to be the most common sensitizing agent in our series, as in those of others (Freier *et al.*, 1969; Ratner *et al.*, 1958). However, it is difficult to say how often the patients may develop other sensitivities, because in the beginning, during the most sensitive period, all our patients were fed with human milk only. If all infants were fed from the outset with, say, soya milk, the incidence of soya sensitivity would doubtless increase considerably. With the elimination diet the clinical course was usually favourable, resembling the improvement seen in coeliac disease treated with a gluten-free diet. At first the clinical symptoms disappear, then absorptive function normalizes, and finally, ½–1½ years after the start of treatment the intestinal mucosa becomes completely normal. Clinical sensitivity to cow's milk disappears at the age of about 1 year, and often before complete recovery of the intestinal mucosa. Mucosal healing continued even when the patients were fed on cow's milk once they were able to tolerate it clinically.

Follow-up studies clearly show that this disease is transient and complete recovery follows. It was suggested earlier by us (Visakorpi and Immonen, 1967) that cow's milk intolerance may 'pave the way' to permanent gluten intolerance, i.e. to coeliac disease. The present series included 5 coeliac patients, but we believe that these patients initially had coeliac disease, which was then complicated by cow's milk intolerance. The misconception that cow's milk intolerance may induce coeliac disease was due to the fact that it may be accompanied by 'transient gluten intolerance' as well as by intolerances to other food proteins. If this transient intolerance to gluten is unrelated to coeliac disease, as we now believe, does that also mean that coeliac disease in early infancy is often associated with cow's milk intolerance? If we add these 5 patients with cow's milk intolerance to our whole series of infants with confirmed coeliac disease (82 infants) we find a high incidence of cow's milk intolerance in coeliac disease. If we count only the coeliac patients in whom the disease set in before 6 months of age, the incidence is higher still. For practical reasons a differential diagnosis between coeliac disease and the malabsorption syndrome with cow's milk intolerance should be made as early as possible. In our experience, however, this is difficult. If the patient has never received gluten and the biopsy reveals only minor changes, coeliac disease can be excluded. But if the dietary history

is uncertain and laboratory tests as well as biopsy show severe malabsorption and intestinal damage, the diagnosis can be verified only by clinical observation with biopsies over a period of several years.

The aetiology and pathogenesis of this disease are beyond the scope of this study. We have found that cow's milk (probably cow's milk proteins) exert a deleterious effect on the intestinal mucosa in these patients (Kuitunen *et al.*, 1973). It is evident that immunological mechanisms are involved (Savilahti, 1973), but observed changes in local mucosal immunoglobulin production are transient. In spite of the high frequency of atopic phenomena like eczema and eosinophilia, the reaction in the intestine seemed not to be mediated by IgE.

References

Booth, C. C., Stewart, J. S., Holmes, R., and Brackenbury, W. (1963). Dissecting microscope appearances of intestinal mucosa. *Intestinal Biopsy*, Ciba Foundation Study Group No. 14, p. 2. Ed. by G. E. W. Wolstenholme and M. P. Cameron. Churchill, London.

Fällström, S. P., Winberg, J., and Andersen, H. J. (1965). Cow's milk induced malabsorption as a precursor of gluten intolerance. *Acta Paediatrica Scandinavica*, **54**, 101.

Freier, S. (1973). Paediatric gastrointestinal allergy. *Clinical Allergy*, **3**, Suppl., 597.

Freier, S., Kletter, B., Gery, I., Lebenthal, E., and Geifman, M. (1969). Intolerance to milk protein. *Journal of Paediatrics*, **75**, 623.

Gerrard, J. W., Mackenzie, J. W. A., Goluboff, N., Garson, J. Z., and Maningas, C. S. (1973). Cow's milk allergy: prevalence and manifestations in an unselected series of newborns. *Acta Paediatrica Scandinavica*, Suppl., **234**.

Gryboski, J. D. (1967). Gastrointestinal milk allergy in infants. *Pediatrics*, **40**, 354.

Immonen, P. (1967). Levels of the serum immunoglobulins γA, γG and γM in the malabsorption syndrome in children. *Annales Paediatriae Fenniae*, **13**, 115.

Kamer, J. H. van de, Huininк, H., Ten, B., and Weyers, H. A, (1949). Rapid method for the determination of fat in feces. *Journal of Biological Chemistry*, **177**, 347.

Knowles, J. P. (1962). Excretion of formiminoglutamic acid in steatorrhoea. *Gut*, **3**, 42.

Kuitunen, P. (1966). Duodeno-jejunal histology in malabsorption syndrome in infants. *Annales Paediatriae Fenniae*, **12**, 101.

Kuitunen, P., Visakorpi, J. K., and Hallman, N. (1965). Histopathology of duodenal mucosa in malabsorption syndrome induced by cow's milk. *Annales Paediatrici*, **205**, 54.

Kuitunen, P., Rapola, J., Savilahti, E., and Visakorpi, J. K. (1973). Response of the jejunal mucosa to cow's milk in the malabsorption syndrome with cow's milk intolerance. A light- and electron-microscopic study. *Acta Paediatrica Scandinavica*, **62**, 585.

Lamy, M., Nezelof, C., Jos, J., Frézal, J., and Rey, J. (1963). Biopsy of intestinal mucosa in children. First results of study of malabsorption syndromes. *Presse Médicale*, **71**, 1267.

Liu, H. Y., Tsao, M. U., Moore, B., and Giday, Z. (1968). Bovine milk protein induced intestinal malabsorption of fat and lactose in infants. *Gastroenterology*, **54**, 27.

Ratner, B., Dworetzky, M., Oguri, S., and Aschheim, L. (1958). Studies on the allergenicity of cow's milk. The allergenic properties of alpha-casein, beta-lactoglobulin and alpha-lactalbumin. *Pediatrics*, **22**, 449.

Savilahti, E. (1973). Immunochemical study of the malabsorption syndrome with cow's milk intolerance. *Gut*, **14**, 491.

Visakorpi, J. K., and Immonen, P. (1967). Intolerance to cow's milk and wheat gluten in the primary malabsorption syndrome in infancy. *Acta Paediatrica Scandinavica*, **56**, 49.

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