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Food-Induced Malabsorption Syndromes

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Abstract

ABSTRACT: A syndrome of chronic diarrhea, vomiting, and failure to thrive was described 35 years ago. The syndrome was caused by damage in the jejunum after ingestion of cow's milk. Symptoms appeared in young infants shortly after introduction of cow's milk formula. Patients had moderate steatorrhea, decreased absorption of D-xylose, and, often, iron-deficiency anemia and hypoproteinemia. They had strong IgA and IgG antibodies to cow's milk. IgE antibodies to cow's milk were negative, as a rule. Indicators of cell-mediated immune reaction to cow's milk proteins were often positive. Patients were tolerant to cow's milk by the age of 3 years. Malabsorption was due to damage to the jejunal mucosa: Varying villus atrophy was associated with inflammation in surface epithelium and lamina propria. The epithelial cell renewal rate increased. Surface epithelial cells decreased in height, with short, furry microvilli and large aggregates of lysozymes. The number of intraepithelial lymphocytes was markedly increased, but normalized during cow's milk elimination. Most of these lymphocytes had $[\alpha]/[\beta]$ T-cell receptors, and many were cytotoxic. Some specimens had an increase in $[\gamma]/[\delta]$ T-cell receptor-bearing cells. In the lamina propria, CD4+ cells predominated, and some of them were activated. IgA- and IgM-containing cells were markedly increased during cow's milk exposure, but IgE cells were not abnormal. The density of eosinophils was moderately increased. Secretion of interferon- $[\gamma]$ by cells isolated from patients' intestines was markedly increased. Morphologic and immunologic findings suggest that T-cell-mediated reaction to proteins in cow's milk is present in the small intestines of patients with this syndrome and causes this enteropathy.

DEFINITION

A syndrome of chronic diarrhea, weight loss, and growth failure, similar to that observed in celiac disease but appearing in young infants who had had no cereals in the diet, was described more than 30 years ago by several groups (1–6). Generalized malabsorption, affecting fat and carbohydrates and also other nutrients can be demonstrated by laboratory tests. The malabsorption is not due to deficiency of digestion but to changes in the structure of the intestinal mucosa. The syndrome is cured by elimination of cow's milk. Therefore, in this article this entity, which has several designations in the literature is referred to as an enteropathy induced by cow's milk (EICM). Similar syndromes have been described in association with soy proteins (7,8) and other foods (9).

OCCURRENCE

This type of reaction to cow's milk has always been uncommon. After its recognition, it was observed in our hospital at an average rate of three patients per year (1962–1972), whereas simultaneously the number of infant patients with celiac disease was five times more. During the following 5 years (1973–1977) more infants with slowly developing gastrointestinal symptoms to cow's milk challenge were seen on the average of five patients per year, but at that time many of these infants had normal jejunal structure (10) and no malabsorption syndrome. Since then, this severe type of jejunal damage caused by

cow's milk allergy (CMA) has almost vanished from Finland. During the 1990s we have had 5 patients with this syndrome. The same seems to have happened elsewhere: A similar reduction in EICM was noted in Spain between 1980 and 1987 (11). A search of the medical literature on the syndrome on MEDLINE (U. S. National Library of Medicine) shows a progressive decline of reports on the condition.

Several changes in infant feeding practices in Finland in the 1970s and later are probably responsible for the gradual decrease in the incidence of EICM, even though other forms of CMA occur commonly today in our country (12). Exclusive breast-feeding was at its shortest duration in the early 1970s but gradually became more extended in the late 1970s (13). At the same time, homemade cow's milk-based mixtures were replaced first by unadapted formulas and then rapidly by adapted formulas. The protein content of the adapted formulas was reduced during the 1980s. The changes in nutrition, combined with other rapid changes in society, may have affected the microbial flora of infant intestines, and this may have had an impact on the occurrence of atopic diseases in general (14,15) and also on the appearance of this specific syndrome.

CLINICAL PICTURE

Symptoms appeared within a few weeks after the introduction of cow's milk-containing supplements into the diet. Usually, the duration of full breast-feeding before the first cow's milk feeding was short. On the average, cow's milk-containing foods were introduced into a diet early, at the mean age of 1 month, according to our first study (16), but in the second study, later (10) (Table 1). Affected infants invariably had diarrhea. In most cases, this condition was also associated with vomiting (Table 1). Infants had severe growth retardation, which affected their weight more than their height. In the later series the retardation was less severe.

Study	Number of patients	Sexes (M/F)	Feeding (M/F)	Weight on admission (kg)	Height on admission (cm)	Age at introduction of cow's milk (days)	Age at admission (days)	Age at onset (days)
Uusitalo et al (10)	18	10M/8F	10M/8F	4.5	55	10	10	10
Savilahti et al (16)	36	20M/16F	20M/16F	4.5	55	10	10	10

TABLE 1. Characteristics of patients with enteropathy induced by cow's milk in two studies Data shown in percentages represent percentage of total group affected.

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When the infants were given a cow's milk-free diet, the diarrhea ceased in a week in the great majority of cases, but 3 of 54 infants required prolonged intravenous nutrition.

LABORATORY FINDINGS

Moderate anemia (hemoglobin concentration below 100 g/l) was present in 20% of our series, but in the French series the incidence was higher, 69%[\(17\)](#). Iron deficiency was more common than anemia [\(17\)](#), suggesting that in most cases the anemia was caused by it. Other laboratory tests revealed malabsorption of nutrients including hypoproteinemia and deficiency of vitamin K–dependent factors leading to an increase in coagulation time in 35% to 50%[\(16,17\)](#).

Steatorrhea, demonstrated by increased fecal fat excretion, was found in most cases—in our first series, in 82%. In contrast to patients with pancreatic insufficiency, these patients had only moderate steatorrhea, with absorption of more than 80% of the fat eaten. The D-xylose test result was abnormal in approximately the same proportion. Before elimination of cow's milk, lactose was in most cases undigested. We found it in the urine in 55% and in the stools in 52% of cases. Lactose malabsorption was more common in the youngest infants [\(7\)](#). Soon after cow's milk was eliminated, lactose absorption became normal [\(6\)](#).

Cow's Milk Antibodies

These infants often had increased levels of serum immunoglobulin (Ig) A—in our study, 74%. The IgA levels normalized during cow's milk elimination. They showed precipitating antibodies to cow's milk in a high percentage of cases (65%) [\(16\)](#), and with more sensitive methods, all cases were shown to have cow's milk antibodies [\(17\)](#). A group of patients with EICM was shown to have IgA deficiency [\(16\)](#). As a rule, patients with EICM did not have IgE antibodies to cow's milk. According to a recent study of slow-reacting patients with CMA and diarrhea, none had IgE cow's milk antibodies [\(18\)](#). Results of measurements indicating enhanced cell-mediated immunity to cow's milk proteins are often seen in these patients [\(19\)](#). However, the lymphocyte stimulation test is often positive even in infants with no reaction to a cow's milk challenge test [\(20\)](#). A skin-patch test with cow's milk may be helpful as a screening test for this syndrome [\(18,21\)](#). In these studies, however, gastrointestinal biopsy specimens from the jejunal structure were not studied.

GASTROINTESTINAL FINDINGS

Morphology of the Jejunum

The findings in the jejunal biopsy specimens are like those in celiac disease but, often, less pronounced. There is a varying degree of villous atrophy with crypt hyperplasia and inflammation, both intraepithelially

and in the lamina propria (10,16,17,22). In the series of patients from 1962 through 1973, 50% had subtotal villous atrophy of the jejunum (Table 2); during 1974 through 1977, the proportion declined to 15%. Partial villous atrophy was most commonly seen in that series, but some patients even had normal villous height (10), and it may be inappropriate to include the latter in this syndrome. With reduction in villous height, at the same time the crypts were elongated (10,16), the average number of cells in the crypts being 1.8 times the number in control subjects (23). In English studies, the crypts were also found to be elongated, but owing to the decrease in villous height, the specimens were thinner than normal (22,24). The most sensitive measure of the morphologic change is the villus-to-crypt ratio (25). The morphology of jejunal damage in soy protein–induced enteropathy had characteristics similar to those described for EICM (26).

Study	Number of patients	Subtotal villous atrophy ^a (% cases)	Partial villous atrophy ^b (% cases)	Normal structure of villi ^c (% cases)
Rothen et al. (17)	32	3 (1)	31 (26)	16 (5)
Koivunen et al. (18)	48	36 (27)	35 (17)	8 (4)
Yaraskas et al. (19)	19	16 (1)	28 (11)	26 (5)

^a Mean villous height less than 150 µm.
^b Mean villous height 150–250 µm.
^c Normal (including specimens with slight changes): mean villous height more than 250 µm.

TABLE 2. Morphology of the jejunal specimens in patients with enteropathy induced by cow's milk^aMean villous height less than 150 µm. ^bMean villous height 150–250 µm. ^cNormal (including specimens with slight changes): mean villous height more than 250 µm.

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Columnar cells of the surface epithelium of the normal jejunum were replaced by crypt cells of a more cuboidal, immature type, their height being reduced by one third (3). With an electron microscope the epithelial cells were seen to bear short, furry microvilli that contained large aggregates of lysozymes, and their nuclei were abnormal (27). The basement membrane was unevenly thickened. We found that the epithelial cell renewal rate was markedly increased as the result of an increased mitotic rate and larger crypt cell compartment (23). In a recent study, both morphology and monoclonal antibody staining associated most strongly with mitotic cells were used to measure mitotic activity in the jejunal crypts. Both methods showed increased mitotic activity in the crypts, although of a moderate degree (28). As a consequence of the immaturity of the epithelial cells, the activities of disaccharidases were low, and most patients also had secondary lactose malabsorption (7,22,29).

In most cases, there was an increase in the number of intraepithelial lymphocytes. We found three times as many lymphocytes intraepithelially as seen in the normal intestine (30), a value that did not differ from that found in untreated celiac disease. During cow's milk challenge, the cell counts did not always increase as much (22). The density of eosinophils in the epithelium on biopsy was increased (24).

Most intraepithelial lymphocytes were CD3+ α/β T-cell-receptor-bearing cells, and, as in normal intestines, they were mostly suppressor-cytotoxic CD8+ cells (31). The proportion of TIA1-positive cells among intraepithelial lymphocytes (UCHL1-positive cells) in specimens from patients with malabsorption in CMA increased and decreased with the duration of the elimination diet (32). TIA1 is a specific cytotoxic granule-associated protein expressed only by T lymphocytes and natural killer cells. Thus, the proportion of cytotoxic cells in the epithelium of these patients was high. The same has been shown for specimens from patients with celiac disease.

In a small series of four patients, all had increased densities of intraepithelial γ/δ -TCR+ cells (33). We have measured the densities of T cells bearing various surface markers in eight specimens from patients with EICM. Four of them had increased density of γ/δ -TCR+ cells in the epithelium (Fig. 1). The increase in this cell type in the epithelium is found regularly in specimens from patients with celiac disease (34) and is not seen in other infantile enteropathies (35). However, as indicated, it is not entirely specific for celiac disease, dermatitis herpetiformis, or latent forms of celiac disease (36).

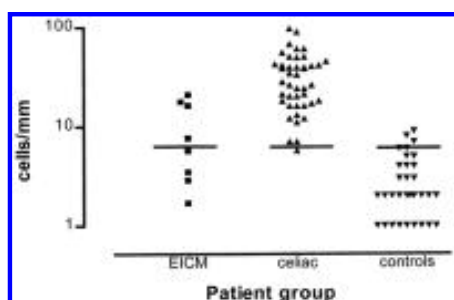


FIG. 1. Density of γ/δ T-cell receptor-positive cells in the epithelium of jejunum of eight patients with enteropathy induced by cow milk (EICM), of 44 patients with untreated celiac disease and 37 control subjects. The mean $\pm$ 2 SD of control subjects is indicated.

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In the lamina propria, the numbers of lymphocytes, plasma cells, and eosinophils were increased (24,37). CD4+ T-helper (Th) cells predominated in the lamina propria, as in normal intestines (31). Many CD4+ cells were also HLA-DR+, suggesting that they were activated. These cells diminished during cow's milk elimination (31). A higher proportion of cells isolated from jejunal specimens of patients with EICM secreted interferon (IFN)- γ and interleukin (IL)-4 than from control specimens (38). The number of IFN- γ -secreting cells was 10 times that of cells secreting IL-4, showing the predominance of the Th1 response in the intestine. The numbers of cells secreting IL-5 and IL-10 were unchanged. In the blood, cytokine-secreting cells were uncommon, but patients with EICM had more cells secreting all four cited cytokines than did control patients (38).

Electron microscopy showed edema in the lamina propria, swelling of the epithelium of the small blood vessels, and degranulation of mast cells, eosinophils, and macrophages (39). The numbers of immunoglobulin-containing cells in the lamina propria increased significantly during positive cow's milk challenge tests; the increase in IgA-and IgM-containing cells was, on average, 2.4 times that seen in prechallenge specimens. In contrast, in specimens from patients who showed no symptoms during challenge, the IgA cells increased 1.5-fold, whereas the IgM cells did not change during 4 to 6 weeks consumption of a cow's milk-containing diet. During a renewed elimination diet, the densities of IgA and IgM cells declined (40). In another study, increases were seen only in IgA-containing cells (41). The presence of IgE-containing cells in the lesion is disputed. We have not seen these cells, either in specimens with villous atrophy or in those with normal structure (40,42), whereas these cells were reported in two other studies (39,43). Shiner et al. (39) also suggested deposition of complement in the intestine at the time of reaction, which we could not verify (44). Using fluorescein-labeled cow's milk proteins, Pearson et al. (45) estimated that 0.5% to 5% of immunoglobulin-containing cells produce antibodies to these proteins. Of specific antibody-producing cells, 70% were IgA isotype-positive and 30% IgE positive. In enteropathy induced by soy, cells containing IgA and IgM were increased at the time of clinical reaction to soy but normalized when soy was eliminated from the diet (26).

Early studies on immunoglobulins and complement in the intestines of patients with this syndrome argued against a primary defect in B-cell function in the syndrome. The strong local reaction during exposure to cow's milk was probably an attempt to exclude cow's milk antigens, although unsuccessful, because there was a significant increase in circulating antibodies to cow's milk during the challenge test (40).

The cellular infiltrate of lamina propria was similar to that seen in celiac disease and showed the cytokine secretion pattern characteristic of Th1 cells.

Permeability of the Jejunal Mucosa

Before treatment, the mucosa of patients is permeable in vitro to horseradish peroxidase, a protein molecule with molecular weight of 40,000. However, in specimens taken during cow's milk elimination, the permeability returned to the values seen in control subjects (46). Jejunal specimens from patients reacted to exposure to [beta]-lactoglobulin with an increase in a short current circuit, which was not seen on exposure to human [alpha]-lactalbumin, suggesting that [beta]-lactoglobulin activates chloride secretion (47). The same study showed that jejunal specimens taken before treatment were more

permeable to [beta]-lactoglobulin and degraded it less than specimens obtained from treated patients (47).

DIAGNOSTIC CRITERIA

As in food allergies of all types, the basis of diagnosis is the association of the clinical symptoms with an elimination–provocation trial. I shall discuss only problems specific to enteropathy. The clinical condition of an infant with EICM is often so poor that parenteral nutrition is required for days and even weeks. When there is a strong suspicion of EICM, the condition of the patient should not be endangered by a provocation trial or even an examination of jejunal structure by biopsy. In less severe cases with clinical signs suggesting malabsorption, taking a jejunal biopsy specimen either by gastroscope or with a suction biopsy capsule is highly informative. If the lesions described above are seen, the major diagnostic difficulty is to differentiate between EICM and other protein-induced enteropathies, particularly celiac disease. If the infant has never had gluten-containing cereals in its diet, the dietary history may be clear enough to exclude celiac disease. Further, celiac disease–specific autoantibodies are not seen in patients with EICM (48). Counting intraepithelial [gamma]/[delta]-TCR+ cells is helpful; if they are low, celiac disease is highly unlikely. A normal density of [gamma]/[delta]-TCR+ is also seen in infantile autoimmune enteropathy (35), which occasionally is difficult to differentiate from EICM. Most patients with autoimmune enteropathy have specific autoantibodies, and diarrhea is not responsive to elimination of nutrients (49).

In unclear cases, in addition to cow's milk, gluten-containing foods should be eliminated from the diet. Only a long dietary manipulation and follow-up will disclose which patients initially had, or later on, had development of celiac disease in association with EICM. In our series, 7 of 54 infants with cow's milk challenge–proven EICM, manifested celiac disease when their diets were normalized, as shown by a jejunal biopsy specimen taken after a prolonged consumption of a gluten-containing diet (16).

PROGNOSIS

Patients with EICM lose their hypersensitivity to cow's milk at an early age. At the age of 2 years, all the patients in our early study could tolerate cow's milk and, on average, tolerance developed at the age of 55 weeks (16). In less severe cases, diagnosed later, tolerance developed at a later age; however, all of these patients were drinking cow's milk at the age of 3 years (10). Clinical tolerance seemed to develop more rapidly in the latter patients than in unselected patients seen with CMA today. Among 118 patients

with predominantly skin symptoms, 50% tolerated cow's milk after being on an elimination diet for 1 year and 68% after 2 years on an elimination diet (Saarinen and Savilahti, unpublished results, 1999).

PATHOGENESIS

Morphologic and immunologic studies of the intestinal mucosa in EICM indicate that jejunal damage and therefore the syndrome are caused by enhanced cell-mediated immune reaction, most likely to antigens derived from cow's milk. Experimental work has shown that T cells, when activated, cause damage similar to that observed in EICM (50). A well-studied model for such a reaction is celiac disease, in which the initiators of the cell-mediated reaction are T cells reactive with gluten transformed by tissue transglutaminase (51). In celiac disease, gluten peptides are presented to T cells by a limited number of HLA-DQ heterodimers; therefore, celiac disease is closely associated with certain HLA class II antigens (52). No such association could be found for EICM (53). This could mean that the antigens initiating a T-cell reaction in the intestine in EICM are more varied than in celiac disease. Factors shifting the immune response to a strong Th1-type reaction and inhibiting the development of tolerance, which usually takes place for food antigens, can only be speculated. Another interesting point in the pathogenesis of EICM is its relation to other forms of allergic reaction to cow's milk: Is the early development the same for different types of hypersensitivities or do they develop diversely, starting from the moment the infant comes in contact with cow's milk proteins?

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TABLE 1

Study	Number of patients	Chronic diarrhea (%)	Vomiting (%)	Mean weight on admission (in SDs)	Mean height on admission (in SDs)	Eczema (%)	Mean age at introduction of cow's milk (wk)	Mean age at admission (wk)	Means age when tolerating cow's milk (mo)
Kuitunen et al. (16)	54	100	67	-3.3	-1.4	22	5	15	12.7
Verkasalo et al. (10)	28	79	64	-2.0	-0.7	11	6.7	10.7	17.0

Data shown in percentages represent percentage of total group affected.

TABLE 1. *Characteristics of patients with enteropathy induced by cow's milk in two studies*Data shown in percentages represent percentage of total group affected.

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TABLE 2

Study	Number of patients	Subtotal villous atrophy ^a (% cases)	Partial villous atrophy ^b (% cases)	Normal structure of villi ^c (% cases)
Baudon et al. (17)	32	3 (1)	81 (26)	16 (5)
Kuitunen et al. (16)	48	56 (27)	35 (17)	8 (4)
Verkasalo et al. (10)	19	16 (3)	58 (11)	26 (5)

^a Mean villous height less than 150 μm .

^b Mean villous height 150–250 μm .

^c Normal (including specimens with slight changes): mean villous height more than 250 μm .

TABLE 2. Morphology of the jejunal specimens in patients with enteropathy induced by cow's milk^aMean villous height less than 150 μm .

^bMean villous height 150–250 μm .^cNormal (including specimens with slight changes): mean villous height more than 250 μm .

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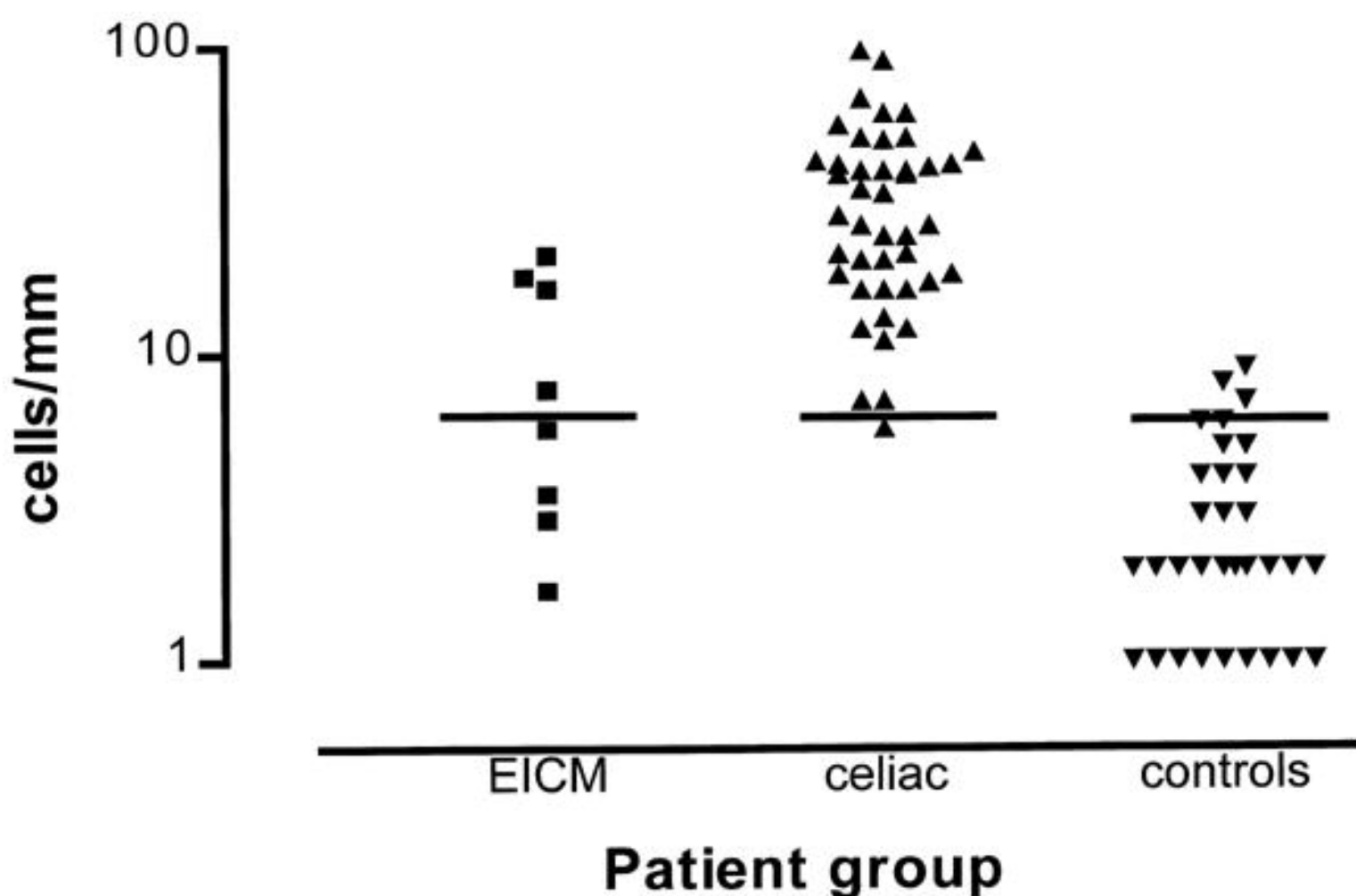
FIG. 1

FIG. 1. Density of γ/δ T-cell receptor-positive cells in the epithelium of jejunum of eight patients with enteropathy induced by cow milk (EICM), of 44 patients with untreated celiac disease and 37 control subjects. The mean $\pm$ 2 SD of control subjects is indicated.

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