Case report

Combined cow's milk protein and gluten-induced enteropathy: common or rare?

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SUMMARY A child is reported with unequivocal gluten and cow's milk protein-induced enteropathy. This is believed to be the first reported case of this association.

At least six commonly ingested proteins can induce gastrointestinal symptoms and/or small intestinal mucosal damage – namely, gluten, cow's milk protein, soya protein, chicken protein, fish protein, and rice protein.¹⁻⁵ With the exception of gluten, the 'intolerance' is generally accepted as being transient, resolving spontaneously by the age of approximately 2 years. Although combined gluten and cow's milk protein intolerance has been reported in the literature⁶⁻⁸ an enteropathy induced independently by each protein has never been proven by systemic dietary manipulations combined with carefully-timed morphological studies.

In this paper, we report a child with unequivocal gluten and cow's milk protein-induced enteropathy. As far as we are aware this is the first documented case of this combined disorder.

Methods

Jejunal biopsies were obtained just distal to the ligament of Trietz, under fluoroscopic control. They were fixed in neutral buffered formalin, embedded in paraffin wax, and 5 µm sections were stained with the periodic acid Schiff technique for microscopic assessment. Interepithelial lymphocytes were quantified by the method of Ferguson and Murray.⁹

Case report

The patient is the only child of unrelated parents who was born at term after a normal pregnancy and delivery weighing 2.9 kg; there was no family history of atopy. She was exclusively breast-fed until 3 months of age when gluten-containing foods were

introduced, and at 5 months cow's milk was introduced. At 6 months she began to vomit, became irritable, developed loose stools and abdominal distention. At the age of 10 months when her weight had fallen to below the third centile, a jejunal biopsy showed the appearance of subtotal villous atrophy (Figure (1)). A strict gluten-free diet was instituted but her symptoms persisted and she continued to lose weight and, at 12 months, she was readmitted to hospital. During this two-month period she had lost a further 0.5 kg despite strict adherence to her gluten-free diet which was confirmed by a careful dietetic history from her intelligent mother. A second biopsy, two weeks after withdrawal of cow's milk protein from the diet showed the appearances of severe partial villous atrophy (Figure (2)). The gluten-free diet and cow's milk protein-free diet were continued and she subsequently became asymptomatic and thrived. Cow's milk protein was reintroduced four months later without recurrence of symptoms. Three months later a pre-gluten challenge biopsy was performed but this again showed subtotal villous atrophy (Figure (3)). Cow's milk protein was again withdrawn and repeat biopsy six months later was entirely normal (Figure (4)). Since that time cow's milk protein and gluten have been independently reintroduced on a series of occasions and both have induced morphological abnormalities which have reverted to normal after they have been withdrawn from the diet (Figs (5-10)).

During this series of dietary manipulations and biopsies she remained completely asymptomatic.

At the age of 7 years she is receiving both a gluten-free diet and a cow's milk protein-free diet and is in excellent health, her height being on the 25th centile and her weight between the 25th and 50th centiles.

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Received for publication 13 April 1982

Table Inter-epithelial lymphocyte counts

Biopsy	Morphology	Lymphocytes per 100 epithelial cells
1	STVA	52
2	SPVA	30
3	STVA	19
4	N	14
5	STVA	37
6	N	16
7	SPVA	25
8	N	9
9	PVA	18
10	PVA	28
		(Normal range 6–20)

INTEREPITHELIAL LYMPHOCYTES (Table)

With the exception of biopsy 3, there was a reasonably good correlation between the severity of the morphological abnormality and the number of interepithelial lymphocytes.

OTHER INVESTIGATIONS

The following investigations were normal: haemoglobin, total and differential white blood count, serum proteins (total and albumin), calcium, magnesium and phosphate, liver function tests (bilirubin, ALT and AST), radiographs of the chest; serum IgG, IgA, IgM, and IgE, yeast opsonisation, C₃, total haemolytic complement, gel diffusion test for precipitins using whole milk protein negative, serum IgE antibodies to β -lactoglobulin and BSA; there was no reaction to skin testing with house mite, lamb, pork, beef, pollen, timothy grass, whole cow's milk, whole egg, wheat, or aspergillus fumigatus.

The following investigations were abnormal: barium studies showed a coarse mucosal pattern in the jejunum consistent with malabsorption, and serum iron was 7.0 μ mol/l (normal 14–22).

Discussion

In 1967 Visakorpi and Immonen⁷ reported 40 infants with malabsorption and suggested that both cow's milk protein and gluten were contributory factors in eight of the patients. The diagnosis was made on the basis of elimination diets with subsequent provocation tests. Careful sequential biopsies after periods of dietary withdrawal and reintroduction of cow's milk protein and gluten were not, however, performed in any of the eight patients. Kuitunen *et al.*⁸ reviewed a group of 54 infants with cow's milk protein intolerance, some of whom had been reported earlier in the paper cited above.⁷ Symptoms attributable to cow's milk protein had resolved by about 1 year of age, and the

children were rebiopsied at 2 years when receiving a cow's milk protein and gluten-containing diet. Morphological abnormalities persisted in nine patients despite an apparent clinical remission, and five of these had subtotal villous atrophy. It was assumed that these five patients had coeliac disease and a gluten-free diet was reinstituted. Despite this, recovery of the mucosa took a number of years, and in two children recovery was only partial, even after up to five years on a gluten-free diet. The possibility of continuing cow's milk protein intolerance as well as gluten intolerance was not considered, and the authors state that in their patients with cow's milk protein intolerance, 0.5–1.5 years after treatment, the intestinal mucosa becomes completely normal. In the light of our experience it appears that this may not necessarily be the case.

The term cow's milk protein 'intolerance' implies clinical symptoms after ingestion of cow's milk protein and improvement on withdrawing the protein, and forms the basis of the recommended diagnostic criteria of Goldman *et al.*¹⁰ These criteria do not take into account cow's milk protein inducing an enteropathy in the absence of any symptoms as was the case in our patient, and also as reported by others.² Lack of clinical symptoms does not, therefore, exclude an enteropathy secondary to cow's milk protein, and this has had an important impact on recently proposed criteria for the diagnosis of cow's milk protein intolerance.^{3 11 12}

It is generally accepted that the symptoms of cow's milk protein intolerance resolve by the age of 2 years, and that a normal diet is well tolerated thereafter. In the complete absence of symptoms cow's milk protein can, however, continue to cause damage to the small intestinal mucosa: in our patient up to nearly the age of 7 years at the time of writing. The findings in our patient raise some important questions: how common is asymptomatic cow's milk protein-induced enteropathy? Is cow's milk protein-induced enteropathy always a transient disorder? What might be the long-term sequelae? These are relevant questions, as the presenting, and only, feature of mucosal damage by another dietary protein (gluten) may be short stature which responds dramatically to a gluten-free diet.¹³

Another intriguing question is whether the cow's milk protein and gluten-induced enteropathy in our patient resulted from two independent aetiological processes, or whether they were related. Finally, it is of interest to note that there was no familial or investigatory evidence to suggest that the enteropathy was allergic in origin.

We are grateful to Dr Judith Darmady for referring the patient to us, and to our Department of

Immunology for performing some of the more relevant investigations.

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