

REVIEW

Milk intolerance in children

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Introduction

Milk intolerance in children in general results from two broad causes namely lactose intolerance and cow's milk protein intolerance sometimes called cow's milk allergy. There has in the past been confusion about these two mechanisms and the need to distinguish the one from the other. In fact in the one individual they may coexist. Thus an infant with cow's milk sensitive enteropathy may also have lactose intolerance resulting from the small intestinal mucosal damage induced by cow's milk protein [1].

Lactose intolerance

Lactose intolerance may be primary or secondary. The primary forms consist first of the excessively rare syndrome of congenital alactasia. There have been remarkably few of these cases reported [2, 3]. Most have in fact been reported from Finland [4]. The vastly more common primary lactose intolerance is the late onset or racial lactose intolerance. This first manifests between the ages of 4 and 18 years and affects most people other than caucasians in adult life [5].

Secondary lactose intolerance

Lactose intolerance may occur as a transient phenomenon in a wide variety of diseases of the small intestine in childhood. These include gastroenteritis, cow's milk sensitive enteropathy, coeliac disease, giardiasis, massive small intestinal resection, immuno-deficiency syndromes and possibly in association with protein energy malnutrition. It has been presumed that the superficial localization of disaccharidase activity on the surface membrane of the microvilli of the enterocyte makes this activity especially vulnerable to any disorder that damages the small intestinal mucosa. However, lactase activity seems to be more vulnerable to damage than the other disaccharidase enzymes. This relative fragility of lactase has been well established e.g., in studies of *in vivo* rates of hydrolysis in patients with generalised intestinal dysfunction caused by tropical sprue, hydrolysis of sucrose and maltose were reduced by 40–50% whereas hydrolysis of lactose depressed by 75%.

In addition to its relative sensitivity to intestinal injury, lactase activity often remains depressed for a longer time after an insult than does that of either sucrase or

maltase. The reasons for this vulnerability are not clear.

It is difficult to determine the incidence of secondary lactose intolerance because, at present, there is no general consensus on the method that should be used to diagnose the condition. In infancy the classical method has been to test watery stools for excess reducing substances. In older children and adults some authorities recommend the breath hydrogen test.

Cow's milk protein intolerance

Cow's milk ingestion may cause a variety of extraintestinal features in infancy such as eczema and asthma but this account will be largely confined to those disorders where milk has caused gastrointestinal symptoms principally. Reactions to milk may be divided into those with a quick onset and those with a slow onset of symptoms.

Quick onset reactions

Anaphylaxis. Acute anaphylaxis is the most serious of the quick onset gastrointestinal food reactions. Anaphylaxis results from a generalized immediate IgE-mediated reaction following the introduction of sufficient antigen into a previously sensitized individual, thereby releasing histamine and other biologically active mediators from sensitized mast cells. This phenomenon of an acute anaphylactic reaction to cow's milk represents the most severe extreme of the clinical spectrum of gastrointestinal food allergic disease [6] and may even result in death [7].

Vomiting, diarrhoea and abdominal pain. Acute vomiting with or without diarrhoea and frequently accompanied by extra gastrointestinal symptoms following cow's milk ingestion is commonly the presenting feature of such quick onset gastrointestinal reactions. Such reactions occur within minutes to an hour of the food being ingested with often only small amounts of milk needed to produce such a reaction. These reactions may occur at the first exposure to cow's milk the child having been previously sensitized via the breast milk [8] or even *in utero* [9].

Some entirely breast-fed infants are exquisitely sensitive to cow's milk. Small amounts of cow's milk given as a complement feed or in solids may lead to the rapid onset of vomiting which will cease when cow's milk is completely withdrawn from the diet. Often such vomiting may be accompanied by the onset of eczema. In some infants the lips and tongue may swell immediately upon contact with cow's milk and this oedema is sometimes associated with urticaria and angioedema which may in fact be the major presenting clinical problem. Characteristically these children have increased levels of total serum IgE and elevated milk specific-IgE antibodies [10] which can be demonstrated by skin-prick test and RAST responses. They also tend to have lower titres of IgG, IgA and IgM cow's milk antibodies than do infants who develop cow's milk protein intolerance some months after they have been fed with cow's milk [11].

Slow onset reactions

Slow onset reactions are much more difficult to diagnose because of the difficulty of associating symptoms with a food taken hours or even days before. However, in general the pathology is more site-specific. The problem is usually one of establishing whether or not the observed gastrointestinal pathology is in fact caused by an adverse immunological effect to a food. Here elimination of cow's milk and its subsequent reintroduction into the diet as food challenge is at the heart of the diagnostic approach.

Pathogenesis. It is probable that there are two syndromes, a primary disorder of

immunological origin and a secondary disorder, a sequel of mucosal damage which in turn produces an immunological abnormality. It seems probable that abnormal handling of dietary antigens across the intestinal mucosa occurs in infants with this disorder. This may be related to a temporary immunodeficiency state such as transient IgA deficiency [12], or to non-specific mucosal damage from any cause. There is evidence that acute enteritis may be followed by not only lactose intolerance but by more persistent and longer lasting cow's milk protein intolerance [1, 13]. Unlike coeliac disease HLA status is normal in this disorder, suggesting that environmental factors are more important than genetic ones [14].

Pathology. In the majority of patients with slow onset of symptoms after cow's milk ingestion the architecture of the proximal small intestinal mucosa is abnormal but the severity of the enteropathy is variable; in some early reports the mucosa was flat and indistinguishable from that seen in coeliac disease [14]. More recently from the same centre less severe mucosal damage has been characteristic [15]. Typically the mucosa in untreated cow's milk sensitive enteropathy is thin [16] and the pathological changes are patchy [17]. The intraepithelial lymphocytes are increased although not to the levels found in untreated coeliac disease [18]. There is also often a dense accumulation of fat in the epithelium which is a particular feature of this disorder and the post-enteritis syndrome [19]. The mucosa rapidly returns towards normal or near normal on withdrawal of cow's milk, only to relapse following challenge with milk [20]. However unlike coeliac disease the mucosa remains thin throughout [16] and the intraepithelial lymphocytes fall to levels below normal on a milk-free diet rising to levels within normal limits after cow's milk challenge [18].

Clinical features. Presentation may be acute with vomiting and diarrhoea, or as a chronic syndrome characterized by less severe vomiting and diarrhoea with failure to thrive. The majority present with acute symptoms under the age of 6 months and at time of onset, have features indistinguishable from acute infective enteritis. It may practically be very difficult to determine whether the syndrome began as an acute gastrointestinal infection. Lactose intolerance may accompany protein intolerance but it is relatively short lived.

There is usually a latent interval between the introduction of cow's milk and the onset of symptoms. These chronic syndromes may present in a very similar fashion to coeliac disease with loose stools and failure to thrive. Cow's milk protein intolerance may also be associated with iron deficiency anaemia due to intestinal blood loss (either occult or overt). This is related to an endoscopic colitis [21, 22].

Diagnostic criteria

Because of its transient nature it may be difficult to fulfil all the diagnostic criteria for cow's milk sensitive enteropathy as for coeliac disease; nevertheless accurate diagnosis is important. It is important to exclude an infective cause of the enteropathy although infection and cow's milk protein intolerance may coexist. As with all dietary protein intolerances, diagnosis is based upon the response to withdrawal and reintroduction of the offending protein and there is no specific laboratory test apart from serial biopsy related to elimination and challenge. The finding of a patchy enteropathy with a thin mucosa in a cow's milk fed infant, who responds rapidly to a cow's milk elimination diet provides firm presumptive evidence for this diagnosis. Such children may be described as having a milk elimination responsive enteropathy. The transient nature of this disorder as well as the desire to avoid early milk challenge (because of the potential

risk of acute anaphylaxis) leads in practice to a late milk challenge at the age of 9 months to 1 year. These children may then no longer be milk intolerant at the time of milk challenge (i.e., at age of 9–12 months). Milk provocation in such circumstances merely establishes the safe return of cow's milk into the diet. It does not confirm the diagnosis of a cow's milk sensitive enteropathy. In practice it is not necessary to have this final confirmation of the diagnosis.

Relationship to soy protein intolerance

It has also been established by Ament & Rubin [23] that soy protein may damage the small intestinal mucosa and indeed a number of other foods in early infancy have been established in this way to damage the small intestinal mucosa usually as a sequel to cow's milk sensitive enteropathy [24, 25].

When soy formulae are used in infants already cow's milk protein-sensitive, Perkkio *et al.* [26] have shown that there is a 15% risk of developing soy sensitive enteropathy but Wong [27] reported in a much more severe group of cow's milk protein sensitive infants an 80% recurrence of symptoms on soy milk. It is my view that it is unwise to use soy protein when there is already morphological damage to the small intestinal mucosa. All these food sensitive enteropathies are temporary disorders of infancy and do not occur in adult life.

Relationship to gastroenteritis

Cow's milk sensitive enteropathy may occur as a sequel to acute gastrointestinal infection and be an important cause of persistent diarrhoea occurring as a sequel to acute gastroenteritis [1]. Whilst most if not all children have small intestinal mucosal damage at time of acute infection, clearly only a minority of children develop this problem after gastroenteritis. In our current experience only 1.5% [28] develop the classical features of cow's milk sensitive enteropathy but a further 7.5% developed post-enteritis lactose intolerance. This lactose intolerance may in turn be in fact related to infection *per se* for example rota virus infection or to persistent small intestinal mucosal damage due to sensitisation to cow's milk protein which may be of variable duration. It may be also due to a combination of persistent infection, re-infection [29] and to transient food sensitization all occurring together.

I would like to propose that much of delayed recovery after gastroenteritis may be directly related to the way infants are fed i.e., cow's milk protein intolerance and that this in turn is related to the antigenicity of the feed.

Concept of allergenicity of feeds

In developed communities such as ours in London and that in Finland cow's milk sensitive enteropathies and other food sensitive enteropathies occurring *de novo* or as a sequel to gastroenteritis appear to be both a declining problem and, when they do occur, cause less severe small intestinal mucosal damage than was formerly reported.

In Finland Verkasalo *et al.* in 1981 [15] have described this very clearly but have attributed this decline in severity to increased awareness of cow's milk intolerance on the part of the both laymen and the medical profession. Whilst this may play a role I do not believe this to be the principal reason. In our own experience we have morphometric evidence that small intestinal mucosal damage we see now is less severe than it was formerly. Has there been a change in artificial feeding in both these communities? Yes there has been a change from modified to adapted formulae.

Turning to the developing world Wong in 1965 described a very severe form of intractable diarrhoea in Singapore which he now knows to have been a very severe type of cow's milk allergy [27]. He attributed this directly to a decline in breast feeding at that time. Some cases were fatal. The size and severity of this problem have fallen drastically now, with very few cases of chronic diarrhoea and malnutrition in Singapore at all and very few indeed of cases of cow's milk protein intolerance. This is despite a relatively low level of breast feeding and high level of bottle feeding. However it does coincide with a change in artificial feeding from modified to adapted formulae. One major infant feeding company only markets adapted formulae in Singapore now. This change in infant feeding coincides with Singapore's move from a developing to a developed community.

In other developing communities for example Indonesia [17] cow's milk sensitive enteropathy remain a common cause of chronic diarrhoea. It is proposed that when a community changes from old fashioned modified formulae to adapted formulae cow's milk sensitive enteropathy dramatically reduces in frequency and severity.

Is there in fact any prospective evidence that the type of oral feeding given infants after gastroenteritis influences delayed recovery? Manuel & Walker-Smith [17] compared the use of Pregestimil (old formulae, high osmolality), Al 110 and SMA in the immediate feeding of infants after gastroenteritis. The highest level of delayed recovery (presumably related to cow's milk intolerance) occurred with Al 110 namely 24% with 5% to 2.5% respectively for Pregestimil and SMA. The allergenicity of milk feed at the time of acute gastrointestinal infection may be a critical factor in pathogenesis.

Indeed the allergenicity of the cow's milk or other feeding fed at the time of gastroenteritis may be the most important factor in the relative risk for the development of delayed recovery. Animal models may play a useful role in assessing this risk.

The effect of heat treatment upon the allergenicity or antigenicity of cow's milk proteins has been studied for some time. Recently guinea pigs who may be anaphylactically sensitized to cow's milk have been studied in Cambridge as a model to investigate the sensitizing capacities of various cow's milk and other feeding formulae [30]. Significant differences were found in the capacities of individual formulae to anaphylactically sensitize guinea pigs when given by mouth. Evaporated milks lost their capacity to sensitize orally to beta-lactoglobulin and they were also less sensitizing to casein. This suggested that heat treatment accounted for this difference from whole cow's milk. So four SMA products, heat-processed in different ways, were studied. These showed the sensitizing capacity to beta-lactoglobulin and casein was reduced as the heat treatment became more intense and prolonged. Similar results were obtained with goat's milk when heat treated. Thus these differences appeared to relate to the severity of heat treatment that the formulae received during manufacture. However this is a complex subject as severe heat treatment of skimmed milk was shown by Kilshaw *et al.* [31] to have little effect upon its sensitizing capacity in guinea pigs but similar heat treatment to diafiltered whey completely abolished its sensitizing capacity. These authors have suggested that heat treatment of whey may be a simple and logical strategy for producing an hypoallergenic baby milk. *In vivo* assessment of sensitization in the guinea pig has been compared to immunochemical assessment of antigenicity. Kilshaw *et al.* [31] have however found discrepancies between these two methods e.g., liquid concentrate SMA increased antibody binding capacity for casein with the ELISA technique whereas it was less anaphylactically sensitizing in the guinea pigs.

How such heat treatment produces its effect is not clear. Clearly increased digestibility may be a factor. An alternative strategy to heat treatment in order to make a cow's milk formula less sensitizing is to pre-digest it to a protein hydrolysate. This may be a casein hydrolysate as in Pregestimil and Nutramigen or a lactalbumin hydrolysate as in Alfare. Using the guinea pig model the former milk has been shown by McLaughlan *et al.* [32] to be completely non-sensitizing *in vivo* and the latter by Pahud & Schwarz [33] also to be completely non-sensitizing. This is in contrast to other special formulae for example the casein-based formula Al 110 which is very sensitizing and soy formulae and comminuted chicken meat which are sensitizing but to lesser degree.

Comparable results have been reported clinically by Manuel & Walker-Smith [17] comparing the use of Pregestimil Al 110 and SMA in the immediate feeding of infants after gastroenteritis as referred to above.

Pahud *et al.* [34] have gone on to show that trypsin-hydrolysed whey protein and a peptide preparation produced from the tryptic hydrolysate by ultrafiltration were devoid of sensitizing capacity by the oral route in the guinea pig model. By contrast limited hydrolysis of whey protein leads to an immediate response causing mild systemic anaphylaxis in guinea pigs sensitized to milk proteins, thus suggesting that polyvalent peptide antigens were still present in the limited digest. This experimental work suggests that adapted milks could be made even less sensitizing if trypsin-hydrolysed whey protein were used.

Management of cow's milk protein intolerance

Treatment involves substituting cow's milk feeds with the commercially available cow's milk protein-free formula feeds [35]. Cow's milk substitutes fall into four categories. There are those based on (i) a protein hydrolysate either a casein hydrolysate Pregestimil, and infants over 6 months Nutramigen or a lactalbumin hydrolysate Alfare; (ii) soya protein (Cow and Gate formula S, Prosobee liquid, Prosobee powder, Wysoy); (iii) comminuted chicken which requires supplements with the complete range of vitamins and minerals; and (iv) boiled goat's milk plus vitamins A, D, C, B12 and folic acid tablets (contain lactose) for children over 6 months.

Only those formulae which are nutritionally complete (if necessary with vitamin supplementation) are recommended. Those with a low osmolality should be chosen for young infants or infants with small bowel disease. It is important to ensure that both liquid and solid feeds are free of cow's milk proteins. Lactose intolerance often accompanies the protein intolerance, and in such circumstances lactose should also be withdrawn from the diet. The necessity for dietary treatment is always temporary, and reintroduction of a normal diet is normally nearly always possible by the age of 1–2 years; this is usually achieved in the home, but a history of severe reactions, such as urticaria or anaphylactoid shock, is an absolute indication for reintroduction of a normal diet under very close medical supervision.

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