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REVIEW ARTICLE

Gastrointestinal Allergy to Food: A Review

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SUMMARY

Gastrointestinal food allergy still poses a challenge to the clinician because of its variable symptomatology and lack of reliable diagnostic tests. Its prevalence is estimated at 2~5%, higher in children than in older age-groups. Allergy to food usually diminishes with advancing age. Although a wide variety of foods can cause allergic reactions, cow's milk is the most common cause of food allergy in infants and young children. Depending upon the speed of onset of symptoms, immediate and delayed types of food allergy have been described. Gastrointestinal symptoms in food allergy have been explained by alterations in transport across the intestinal wall (increased secretory and/or decreased absorptive functions), increased permeability, and motility of the intestine. The exact pathogenesis of food allergy is still not clear. However, immediate type of food allergy is believed to be mediated by type I hypersensitivity reaction, involving mast cells and food-specific IgE antibodies. The diagnosis of food allergy is based upon a favorable response to an elimination diet and a response to a challenge with the suspected food. The condition is treated by eliminating the allergenic food from diet for as long as 9-12 months in case of cow's milk allergy. While exclusive breast-feeding for the initial four months or more reduces the chances of development of food allergy, the role of diet restrictions in the mother in reducing the incidence of food allergy in the infant is controversial. Data on food allergy from developing countries are limited. This may be due to lack of diagnosis or less attention given to the condition relative to other diseases including infectious diarrheas and acute respiratory infections. The role of cow's milk allergy in the pathogenesis of persistent diarrhoea, a major problem in the developing world, remains speculative. Frequent intestinal infections and reduced secretory IgA, which are associated with malnutrition, alter intestinal permeability and result in an increased uptake of food antigens. The increased antigenic load combined with factors such as an atopic predisposition may initiate an abnormal mucosal immune response resulting in chronic enteropathy.

Key words: Food hypersensitivity; Food; Gastrointestinal diseases; Diarrhoea

INTRODUCTION

Due to controversies in definition, protean manifestations of the disease and lack of reliable diagnostic tests, gastrointestinal food allergy remains a challenging problem in paediatric practice. This review summarizes the literature on gastrointestinal food allergy. Food allergy is defined as an adverse clinical reaction due to any type of abnormal immune response resulting from the ingestion of a food or food additive (1). While over 140 different foods have been shown to produce allergic reactions in humans, foods most often documented as a cause of allergy are cow's milk, hen's eggs, legumes (especially peanuts), shrimp, oysters, tomato, chocolate, nuts, and seeds (2). The allergenicity of a particular food is influenced by the manner in which the food is prepared, processed, or stored. For

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example, heating of cow's milk denatures certain component proteins and alters its allergenicity (3). Denaturation may either reduce allergenicity or increase it by breaking down proteins and exposing epitopes not usually accessible in the intact protein.

Common Food Allergens

Cow's milk: Cow's milk contains more than 25 proteins capable of inducing a specific antibody response in humans (4). The most allergenic component of cow's milk is β-lactoglobulin, followed by casein, α-lactalbumin and bovine serum albumin (BSA) (Table) (5, 6). Immunoelectrophoretic analysis has shown that casein retains its antigenicity after being heated at 120 °C for 15 minutes, β-lactoglobulin and α-lactalbumin retain theirs up to 100 °C, while BSA and gammaglobulin lose most of their antigenicity between 70 °C and 80 °C (7).

Table: Characteristics of main protein components of cow's milk

Protein component	Molecular weight (kD)	Percent of total protein	Allergenicity	Stability at 100 °C
β-lactoglobulin	18.3	10	+++	++
Casein	20-30	82	++	+++
α-lactalbumin	14.2	4	++	+
Serum albumin	67	1	+	+
Immunoglobulins	160	2	+	+

Hen's egg: Ovalbumin accounts for approximately 65% of the total protein content of hen's egg, and is the most allergenic of all egg proteins as demonstrated by radioallergosorbent test (RAST) studies and histamine release experiments (8). Ovalbumin is relatively heat-labile and, therefore, in patients reacting to cooked eggs, the heat-stable component ovomucoid may be the offending allergen (9).

Legumes: Peanut, known for its potential to elicit severe, life-threatening reactions, is highly heat-stable, maintaining its allergenicity even after being roasted at 145 °C for one hour (10). Peanut oil, containing only peanut lipid and hydrolyzed peanut protein, shows little or no allergenic activity (11). Soybean is a potent allergen which can cause anaphylaxis in sensitized subjects. Soybean oil, like peanut oil, is non-allergenic to soybean sensitive individuals (12).

Fish and shellfish: Fish allergy usually causes urticaria, angioedema, asthma or a combination of these in sensitized subjects within minutes of ingestion. Allergy to fish is easier to diagnose than most other food allergies because of the immediacy of the reaction. The most completely characterized fish allergen is codfish allergen M. It is highly allergenic and cross-reacts with allergens found in other species of fish (13). Shrimp contains potent allergens, and a number of anaphylactic reactions to these allergens have been reported.

Cereals: Wheat flour can result in wheat allergy upon ingestion and baker's asthma upon inhalation, while the gluten fraction is the cause of celiac disease or gluten intolerance. Sutton *et al.* determined that wheat allergy, baker's asthma, and gluten intolerance are each caused by different wheat protein components (14).

Cross-Reactivity of Food Allergens

Foods of the same biological family sometimes share identical or similar epitopes, and may induce cross-reactions in sensitive subjects. Immunologic relationships exist between α-casein, β-lactoglobulin and α-lactalbumin in cow's and goat's milk, which explain the cross-reactivity noted between the two types of milk (15). Cross-reactivity has also been observed between eggs of different birds (16), between different seafoods (17), and between pollens, vegetables and fruits (18).

Epidemiology of Food Allergy

The true prevalence of food allergy is unknown because we lack objective, reproducible methods for diagnosing this condition (19). A study from Finland has given a conservative estimate of a 2~5% prevalence in the population, with a higher prevalence (up to 27%) in children (20). Among adults in the general population, a prevalence of 0.2% has been estimated (21).

Cow's milk is the most common food causing allergy in infants and young children (9). The estimated prevalence of cow's milk allergy (CMA) is between

0.5~7.5% (22, 23). CMA is primarily a disease of infancy and early childhood, although well-documented cases of CMA have also been described in teenagers and adults (24). CMA can also rarely occur after years of asymptomatic ingestion of cow's milk. As with other allergic disorders, a familial tendency has been observed (25). The high prevalence of CMA in infancy and childhood is probably due to a number of factors: (a) immaturity of the immune system as well as of the mucosal barrier of the gastrointestinal tract, (b) increased consumption of cow's milk relative to body weight by infants and children, and (c) strong allergenicity of cow's milk proteins (9). Because of its high prevalence, CMA has been the food allergy that has received the most attention from clinicians, researchers, and the general public.

Clinical Types and Manifestations of CMA

Depending upon the speed of onset of symptoms or signs following ingestion of cow's milk, two types of CMA have been defined: immediate and delayed (26, 27). In the immediate type, symptoms appear within one hour of ingestion of milk. If symptoms appear one to 48 hours later, then the CMA is of the delayed type. The former is easier to diagnose on the basis of clinical history and laboratory investigations, e.g. a raised titre of allergen-specific serum IgE antibody. By contrast, a diagnosis of delayed type CMA is difficult to establish because currently available investigations lack sensitivity. Further, the delay between ingestion and manifestations makes a cause and effect relationship difficult to establish (27). The immediate type of CMA is more common, as 40 to 65% of children with CMA show symptoms within one hour of ingestion of cow's milk (5,28).

The most common symptoms of CMA are gastrointestinal, cutaneous or respiratory. The age of the infant at which symptoms start is largely influenced by the total duration of breast-feeding (22). When breast-feeding is of short duration, symptoms usually appear during the first month of life (29), and in 90% by the age of three months (30). In a study of patients with chronic diarrohea due to CMA, the median age at first visit was three months (31). A brief account of the major manifestations of CMA is described below.

Gastrointestinal manifestations: Diarrohea has been reported to occur in 25 to 75% of patients with CMA, while vomiting occurs in 25 to 50%, usually within one hour after ingestion of milk (4). Acute diarrohea is more common than persistent diarrhoea (diarrhoea for more than two weeks) (28), the former being more common in patients with the delayed-type CMA (32). CMA has been suggested to be a cause of infantile colic (33). Protein-losing enteropathy has also been ascribed to CMA (34). A recent study has suggested that CMA may be a cause of chronic constipation in children (35). Cow's milk restriction resulted in resolution of chronic constipation, which reappeared within 40 to 72 hours of milk ingestion. Specific gastrointestinal syndromes of CMA are cow's milk-sensitive enteropathy and cow's milk-sensitive colitis (26).

Cow's milk-sensitive enteropathy: Onset of symptoms occurs within the first six months of life and is uncommon after three years of age. Enteropathy is more frequent in infants born into atopic families and in those exposed to cow's milk during the neonatal period (36). Affected infants ,have diarrhoea and vomiting which usually persist for many weeks. The infants may have other allergic manifestations, including atopic dermatitis, urticaria, or wheezing. Failure to thrive is a marked feature in certain children. The small intestine is mainly affected and an intestinal biopsy is usually abnormal with patchy lesions (37).

Cow's milk-sensitive colitis: This syndrome is characterized by inflammatory changes in the colon and rectum as a result of immune-mediated reactions to ingested cow's milk proteins (38), and occurs almost exclusively in early infancy. Rectal bleeding is the most common sign. Symptoms of diarrhoea with blood and mucus usually appear within a few days or weeks after starting cow's milk or milk formula feeds. Unlike cow's milk-sensitive enteropathy, the large intestine is mainly involved (39). Cow's milk-free diet leads to dramatic improvement and is a good diagnostic and therapeutic tool. This condition has also been reported to occur in exclusively breast-fed infants (40), and is attributed to small amounts of bovine β-lactoglobulin present in the breast milk of certain mothers who drink cow's milk or eat cheese.

Dermatologic manifestations: In a study involving 100 infants with CMA, the most common dermatologic symptom was urticaria, which appeared on ingestion and in some instances upon skin contact with cow's milk (41). Angioedema, subcutaneous swelling caused by an IgE-mediated reaction, involving the larynx and pharynx, may lead to life-threatening upper airway obstruction (36). Atopic dermatitis (AD) has also been associated with CMA. In a double-blind randomized study of 20 children with AD, Atherton *et al.* found that 50% of the children benefited from cow's milk and egg avoidance (42).

Respiratory Manifestations: In one survey, one-third of children with CMA were found to have respiratory symptoms (28). All infants with immediate cutaneous manifestations had acute wheezing episodes after milk ingestion. However, another study using double-blind challenges with cow's milk was able to establish CMA in only 19% of children suspected to have wheezing due to CMA (43). Of those with predominantly delayed gastrointestinal symptoms, lower respiratory tract symptoms were found in more than half of the infants. In older children, bronchial asthma may occasionally be due to CMA (22). A particular variant of CMA, Heiner syndrome, is characterized by chronic lung disease with pulmonary hemosiderosis, anemia, growth failure and precipitins to cow's milk (44).

Anaphylactic shock: The most extreme manifestation of the immediate type of CMA, anaphylactic shock results from a generalized IgE-mediated reaction to cow's milk. It can be caused by less than one milliliter of cow's milk, and begins with sneezing and itching, followed by generalized urticaria, bronchospasm, and vascular collapse, the whole episode occurring within minutes of milk ingestion. The frequency of anaphylactic reactions varies from none to one-third of cases in studies involving patients with gastrointestinal symptoms (40,45). Anaphylaxis is seen more frequently during clinical challenge after a cow's milk free period (5,40).

Other Manifestations: A variety of other symptoms have also been rarely ascribed to CMA, including irritability, hyperactivity, nocturnal enuresis, and insomnia. In a study of eight infants with insomnia, elimination of cow's milk cured all the patients, while a later challenge with cow's milk produced sleeping difficulties in four of them (46). All the infants had high plasma IgE levels, and four of the five tested also had IgE antibodies to β-lactoglobulin.

Natural History

Most food allergies diminish with advancing age. Allergy to cow's milk and eggs is more likely to be of shorter duration than allergy to fish, nuts, and peanuts (47). In a study by Esteban *et al.*, 50% of children with CMA were tolerant by three years of follow-up, while 50% with egg allergy became tolerant after five years. In contrast, 80% of children initially allergic to fish remained allergic to fish after eight years of follow-up (48). In children with food allergy followed for seven years, tolerance developed in 44% of those who were younger than three years at the start of their signs and symptoms, but in only 19% of children older than three years at the beginning of the disease (47). Therefore, it appears that children who develop food allergy before the age of three years achieve tolerance earlier than children who develop food allergy at an older age.

In a recent study involving 100 children with CMA diagnosed at a mean age of 16 months, cow's milk tolerance was demonstrated by two years of age in 28% of children, by four years in 56%, and by six years of age in 78% (49). The incidence of tolerance was greater among children with the delayed than with the immediate type of CMA. Only 25% were found to still be allergic to cow's milk alone at the end of follow-up. As many as 58% of the children had reactions to eggs, 47% to soy milk, and 34% to peanuts. These results should be interpreted with caution since the adverse reactions to foods other than cow's milk were not evaluated with challenge tests. The results, however, suggest that if children with CMA do not respond to dietary exclusion of cow's milk, there remains a possibility that they are reacting adversely to other food proteins. At final follow-up, 40% of patients had asthma, 21% atopic dermatitis, and 43% allergic rhinitis. Therefore, exclusion of cow's milk from the diets of cow's milk allergic children may not prevent further development of atopic disorders. From these observations it is not clear whether independent mechanisms control the development of cow's milk allergy and other atopic disorders.

Pathology

There are no pathological findings unique to CMA. Since the gastrointestinal system is commonly involved, pathological features of the two variants having mainly gastrointestinal manifestations are discussed.

Cow's milk-sensitive enteropathy: Small intestinal mucosal damage is an obvious finding in cow's milk-sensitive enteropathy (50). Although there are reports of normal mucosal findings in patients with cow's milk-sensitive enteropathy (51), this may be due to the patchy distribution of lesions. The enteropathy has been shown to be cow's milk sensitive by serial biopsies after withdrawal of, and subsequent challenge with, cow's milk (52). Histopathological findings in the jejunal biopsy specimens are similar to those found in celiac disease, although less severe. Usually there is patchy villous atrophy with crypt hyperplasia and inflammation both intraepithelially and in the lamina propria (53). The villous atrophy varies in degree from partial to subtotal. The number of intraepithelial lymphocytes is higher than in healthy subjects but not as high as in celiac disease (54). Ultrastructurally, the epithelial cells have short microvilli, abnormal nuclei and an abundance of lysozymes (52). The mucosal disaccharidase and alkaline phosphatase levels have been found to be depleted (37).

Cow's milk-sensitive colitis: On colonoscopy, the colonic mucosa is erythematous and friable with aphthoid ulcers. There is increased nodularity suggestive of lymphoid hyperplasia (38). Microscopically, the overall architecture of the mucosa is well maintained, without features of chronicity typical of inflammatory bowel disease, such as distorted or atrophic crypts, Paneth cell metaplasia, lymphoid aggregates, or diffuse plasmacytosis (55). The most striking histologic feature is the presence of focal infiltrates of eosinophils in the mucosa, particularly in the lamina propria, which resolves after elimination of cow's milk from the diet. Because of subtle similarities in histopathology, this disorder should be distinguished from inflammatory bowel disease on the basis of biopsy findings, clinical course including response to cow's milk elimination, and absence of systemic inflammatory changes (26).

Pathophysiology

The consequence of exposure to food allergens is a complex process that is still not well understood. Experiments in animal models have provided an excellent opportunity to study the effects of food allergen challenges, the results of which help in elucidating the mechanisms underlying CMA. Most of these studies have described the effects of exposure to food allergens in terms of transport across the intestinal wall, permeability, and motility of the intestine (56).

Intestinal transport: Alteration of intestinal transport (increased secretion and/or decreased absorption) contributes to the symptoms of CMA. Intragastric administration of β-lactoglubulin in mice passively sensitized with monoclonal IgE against β-lacto-globulin, resulted in fluid secretion in the lumen (57). Hooded Lister rats sensitized to egg albumin showed a significantly decreased absorption of Na^+, Cl^-, K^+ and water after the antigen was added to a perfused segment of jejunum (58). These changes were accompanied by mucosal histamine depletion, increased histamine recovery from the perfusates, and villous edema (59). Prevention of these changes by doxantrazole, a mucosal mast cell stabilizer, suggested the involvement of mucosal mast cells (60).

Permeability: Increase in permeability to macromolecules is believed to be important in the pathophysiology of CMA. It may occur either as an increase in vascular permeability or in intestinal permeability. Challenge with egg albumin in sensitized Sprague-Dawley rats resulted in increased counts of ^{125}I-labeled rat serum albumin in the gut wall and contents (61). Changes in vascular permeability were accompanied by increased intestinal secretions, goblet cell mucus, and histamine levels (62). In other studies, evidence of mucosal mast cell degranulation was also seen accompanying permeability changes (63), as well as gross damage to the enterocytes after challenge with food antigen in sensitized animals (64). Increased intestinal permeability to normally unabsorbable molecules has been documented in children with CMA (65).

Motility: Substances released from mast cells such as histamine, serotonin, prostaglandins, and leukotrienes cause smooth muscle contraction in sensitized animals

upon challenge with food allergen (66). Altered intestinal motility patterns have been observed after jejunal challenge with food allergen in sensitized rats (67). As the changes were prevented by doxantrazole, the motility responses were attributed to mast cell involvement.

Pathogenesis

Two phases can be recognized in food allergic reactions (68). The first is the triggering phase, in which the food or its components interact with host cells or non-cellular systems. The second phase is the activation of the mediators of inflammation, which determines the nature and extent of the disease. Although the exact pathogenetic mechanisms in CMA are still not clear (69), it is believed that they may involve one or more of the four classic types of hypersensitivity reactions described by Gell and Coombs (70).

Type I, Immediate hypersensitivity: The majority of allergic reactions to foods are thought to be mediated by immediate hypersensitivity, involving mast cells and food-specific IgE antibodies. The mucosal mast cell, by virtue of its location, mediator content, and IgE receptors, plays a major role in the pathogenesis of responses to allergens presented by the oral route (71). Compared to the other types of immune reactions, type I reaction is relatively well understood. It occurs in atopic individuals who produce excessive levels of total and specific IgE antibodies (72). The incidence of this type of reaction is highest in infancy and declines with age. It is characterized by the onset of clinical symptoms within minutes of ingestion of the food to which the individual is allergic.

IgE binds to Fc receptors on the cell membranes of mast cells. Mast cells have a large number of these receptors, 2~5 x 10^5 per mast cell, which have extremely high affinity for IgE binding (73). Upon exposure to allergen, the IgE molecules and their receptors are cross-linked, which acts as a signal for a cascade of cellular events leading to mast cell degranulation and mediator release. In the gut, mediator release leads to increased muscle tone, stimulation of pain fibers, increased mucus production, and increased permeability to macromolecules (Figure) (71). Local recruitment of inflammatory cells may also take place, with possible late phase reactions and inflammation. Tests that are usually positive in this type of reaction are skin tests, detection of specific IgE by RAST, and basophil histamine release (74).

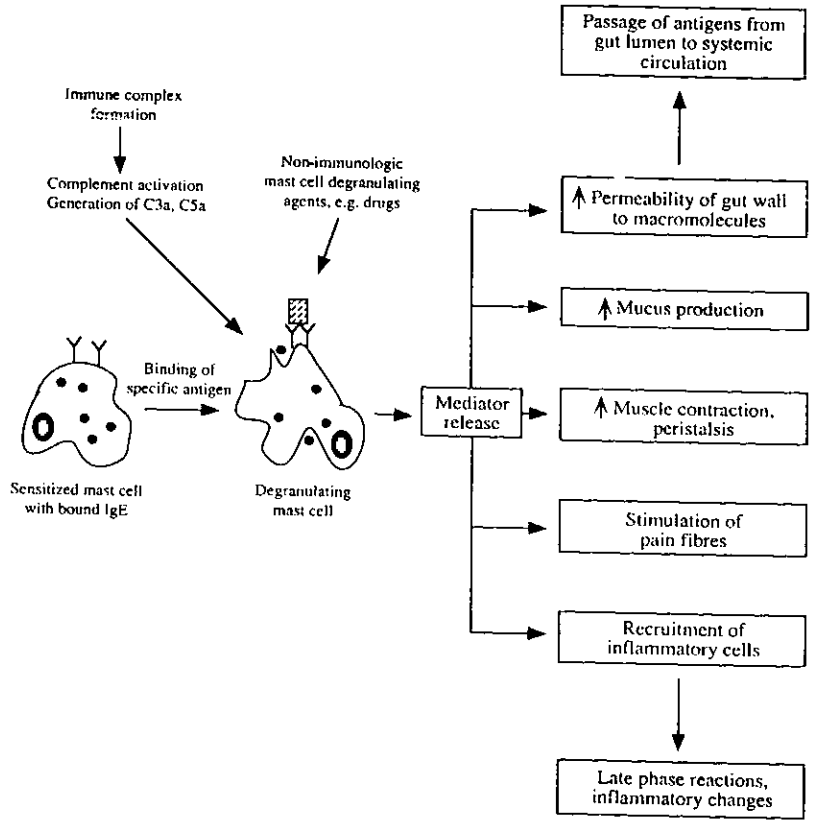

Fig. Activation of mucosal mast cells and its probable local and systemic consequences

Since IgG_4 antibodies can release mediators from mast cells, this subclass has also been implicated in the pathogenesis of immediate hypersensitivity (75). But individuals who have IgG_4 antibodies to food antigens do not have symptoms or positive skin tests unless they also have specific IgE antibodies. On the contrary, a protective "blocking" role for IgG_4 antibodies has also been implicated (76). IgG_4 antibodies are non-complement fixing, non-precipitating, and actually inhibit precipitation by IgG_1 antibodies. An initial IgG_1 response (complement fixing and precipitating) to a food antigen may lead to immune complex disease. Therefore, a progressive change from IgG_1 to IgG_4

antibodies may reduce the harmful effects of continued exposure to the antigen.

Type II, Antibody-dependent cytotoxic hypersensitivity: In this type of reaction, food allergens stick to the surface of cells and are later bound by specific IgG or IgM antibodies. The cells are injured or destroyed by the activation of complement or the release of cytotoxic substances from activated killer cells. Milk-induced thrombocytopenia is probably mediated by this type of reaction (77).

Type III, Immune complex-mediated hypersensitivity: Immune complex reactions usually involve IgG or IgM antibodies that combine with the antigen and form circulating immune complexes to which complement is fixed. When these complexes reach small blood vessels, especially the post-capillary venules, an Arthus-like reaction occurs resulting in vasculitis and tissue damage (4). Based on histologic and immunofluorescent findings in intestinal biopsies, there is evidence that the Arthus-type reaction is involved in the pathogenesis of cow's milk sensitive colitis (78). The finding of immune complex deposits in lung biopsy specimens taken from patients with Heiner syndrome implicates this type of reaction in the pathogenesis of the syndrome (79).

Type IV, Cell-mediated delayed hypersensitivity: Delayed hypersensitivity lesions mediated by CD4+ T-cells are the cause of tissue damage in various diseases, classically in tuberculosis. The reaction is based on the interaction of antigen with endogenous receptors on the surface of primed T-cells. Cytokines are released as a result, which stimulate other types of cells and produce inflammatory changes. A sub-population of T-cells may also be stimulated to become directly cytotoxic (80). The effects of these events are usually delayed and may not be manifested before 24 to 72 hours after antigen exposure. Circumstantial evidence suggests that T-cell-mediated hypersensitivity may play a role in response to food antigens, especially in the delayed type of reactions (81). Recent studies provided inconclusive results as to whether lymphocyte proliferation occurs in response to cow's milk protein antigens in CMA (82).

Recent in vitro studies suggest that cytokines, released by cow's milk protein-stimulated lymphocytes of patients with CMA, may be responsible for the intestinal dysfunctions. Hill *et al.* reported that peripheral T-lymphocytes from patients with the delayed-type CMA produced more interferon gamma (IFN-γ) than those from patients with the immediate type (83). This finding indicates a tendency towards a Th1 type of response in the delayed type. Heyman *et al.* found that peripheral lymphocytes from infants with CMA, when cultured in the presence of cow's milk proteins, released more tumor necrosis factor (TNF-α) than those from control infants (84). Supernatants of lymphocyte cultures from patients altered intestinal barrier capacity, as evident from the decrease in electrical resistance and the increase in horseradish peroxidase, (^{14}C) mannitol, and $^{22}Na^{+}$ fluxes. These results indicate that during CMA the high levels of TNF-α released by lymphocytes increase intestinal permeability.

Diagnosis

In the past, diagnosis of CMA was based upon clinical criteria described by Goldman *et al.* (5): (a) development of symptoms which subside after elimination of milk from diet; (b) recurrence of symptoms within 48 hours of milk challenge; (c) reactions to three such challenges should be positive and have similar onset, duration, and clinical features. The criterion of having three positive challenges is now considered impractical for routine diagnosis, particularly in small infants who are more at risk of having acute anaphylaxis (85). The immediate type of CMA is relatively easier to diagnose with a challenge test, because the amount of food antigen required to produce symptoms is small, and the reaction is rapid and clear. In the delayed type, reactions often appear slowly after a challenge and may require a large amount of antigen (27). Based on these considerations, the two important diagnostic points are a response to an elimination diet and a response to a food challenge (27, 85).

1. *Response to an elimination diet*

This is an absolute criterion for the diagnosis of food allergy, and includes both clinical and laboratory observations. There should be relief of all symptoms and gain in weight if there had been loss of weight due to the disease.

2. *Response to a food challenge*

At present, a single challenge test with food remains the standard for the diagnosis of food allergy. Only natural food (for example, cow's milk but not the isolated proteins) should be used in challenge, because processing may alter allergenicity. The end point of the positive challenge test should be an objective observation, such as vomiting, diarrhoea, colic, erythema, etc. The test should not be done in young infants with severe symptoms because of the danger of anaphylaxis.

Immunological tests

The skin prick test with standardized food extracts, and measuring circulating specific IgE antibodies are sensitive methods which help in the diagnosis of immediate type of allergy (86). The usefulness of these tests is poor in the delayed type of allergy. Moreover, allergen-specific IgE antibodies may persist even when the child has achieved tolerance. Studies evaluating the usefulness of IgG and IgA antibodies to food antigens have yielded contradictory results (28,87,88).

Diagnosis of delayed-type CMA

Because of the delay in appearance of symptoms, the diagnosis of this type of food allergy, i.e. cow's milk-sensitive enteropathy or colitis, can be done on the basis of typical clinical findings, morphologic changes in the intestinal mucosal biopsy specimens, and favoorable response to elimination of cow's milk from diet. Since the danger of anaphylactic reactions is particularly high in this type, a challenge test should be performed late, preferably 9 to 12 months after the beginning of elimination diet (89).

Treatment

The treatment of CMA is based on the elimination of cow's milk and of products containing cow's milk proteins. Elimination should continue for 9 to 12 months. Cow's milk allergic patients with chronic diarrhoea and malnutrition may require prolonged parenteral nutrition because severe intestinal damage may not allow oral feeding for several weeks. For oral feeding, breast milk is best for young infants. Special formulae based on hydrolyzed casein can be given, although they may also cause allergy (90). Children aged more than one year generally do not need special formulae.

Prevention

Interventions, including exclusive breast-feeding, maternal avoidance of allergic foods, and use of "hypoallergenic" formulae, have been attempted to reduce the development of atopic disease in children (91). In a five-year follow-up study, Chandra has shown a significantly reduced incidence of atopic diseases, like eczema, asthma, and food allergy, in infants breast-fed for ≥ 4 months, compared to infants fed cow's milk formula until 6 months of age (92). During 18 months of follow-up, Magnusson *et al.* found no difference in the incidence of food allergy and other atopic diseases between infants whose mothers avoided cow's milk and eggs during the last trimester of pregnancy, and those whose mothers did not (93). In another study, maternal avoidance of cow's milk, eggs and fish during the first three months of lactation resulted in a lower incidence of IgE antibodies to cow's milk and eggs, and also a lower incidence of atopic dermatitis in infants during the first six months of life (94). Because of conflicting results from studies evaluating the role of diet restrictions in the mother in reducing the incidence of atopic disease in the infant, maternal avoidance of food allergens should still be considered investigational (91).

ROLE OF FOOD ALLERGY IN THE PATHOGENESIS OF OTHER DISEASES

Inflammatory bowel diseases

Although infectious agents, genetic and psychogenic factors, and dietary influences have all been implicated, the pathogenesis of inflammatory bowel diseases (IBD) is still unclear. Several observations suggest that allergic reactions may contribute to the inflammatory process. Taylor and Truelove initially raised the possibility of CMA as a pathogenetic factor by observing milk precipitins in the sera of patients with ulcerative colitis (95). Increased numbers of mast cells have been observed in the intestinal biopsy samples from patients with IBD (96). Further, a history of CMA in infancy has been found with increased frequency in patients with ulcerative colitis (97). Exclusion of food allergens by giving elemental or semi-elemental diets

can induce clinical remission in patients with Crohn disease (98). However, some of these observations have been refuted by subsequent studies, and the role of food allergy in the pathogenesis of IBD remains poorly defined (82).

Insulin-Dependent Diabetes Mellitus (IDDM)

Epidemiological studies suggest an association between cow's milk consumption and the incidence of IDDM in childhood (99, 100). Animal studies have also shown that the addition of cow's milk proteins to rat feeds increases the incidence of diabetes in diabetes-prone BB rat (101). Over the last six years, several studies have reported increased levels of circulating IgG or IgA antibodies to cow's milk, β-lactoglobulin, and BSA in children with IDDM (102, 103, 104, 105). BSA has been implicated as a possible trigger of the autoimmune response that destroys pancreatic beta cells in genetically predisposed individuals, causing IDDM (106). BSA shares a common epitope with p69, a pancreatic beta cell surface protein, 69 kD in size. The anti-BSA antibodies found in the sera of patients with IDDM bind to p69, giving rise to a cross-reactive immune response.

Gastrointestinal Allergy to Food in Developing Countries

Most of the literature on gastrointestinal allergy to food comes from developed countries, and data from developing countries are scarce. Whatever data there are from the developing world, come mostly from South-east Asia (37,53,107). Till date, there is no published data about the prevalence of food allergy in Bangladesh. The lack of data may be due to under-diagnosis and less attention given to food allergy relative to other killer diseases, such as acute respiratory infections and diarrhoea.

Persistent diarrhoea and malnutrition are mostly encountered in children of developing countries. The pathogenesis of persistent diarrhoea, which accounts for about ten percent of all diarrhoea episodes but is associated with 30 to 50% of all diarrhoeal deaths, is still not clear (108, 109, 110). CMA has been attributed to be one of the probable causes of persistent diarrhoea. As a result of frequent intestinal infections and reduction in secretory IgA, which are associated with malnutrition (111), the intestinal permeability is altered and there is increased uptake of food antigens (112). The increased antigenic load combined with factors such as an atopic background and age at weaning may initiate an abnormal mucosal immune response resulting in chronic enteropathy and persistent diarrhoea. Much more remains to be known about this important issue.

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