

Clinical Features of Food Allergy in Infants

Emerita Brigino and Sami L. Bahna*

*Division of Allergy and Immunology, All Children's Hospital,
University of South Florida, Saint Petersburg, FL 33701*

Introduction

The manifestations of food allergy vary widely and may involve multiple organ systems (Table 1). The symptoms are mostly non-pathognomonic, which often result in misdiagnosis, performance of unnecessary tests, inappropriate treatments, and unfavorable psychosocial and financial impacts. This article about clinical features of food allergy in infants deals with adverse food reactions that are immunologically mediated.

The wide spectrum of food allergy manifestations may result from different underlying immunologic mechanisms (1). Type I hypersensitivity reactions are IgE-mediated and occur within a few minutes to a few hours. The presenting manifestations may include urticaria, angioedema, atopic dermatitis, vomiting, diarrhea, rhinitis, wheezing, and systemic anaphylaxis. Type II or cytotoxic reactions are mediated by IgG or IgM antibodies that react with a specific antigen on the cell, resulting in complement activation and cytolysis. The rare condition of milk-induced thrombocytopenia is probably mediated by this type of reaction. Type III or immune-complex reactions involve IgG, IgM, IgA, and occasionally IgE antibodies combining with antigen and forming immune complexes to which complement is fixed. These complexes reach the postcapillary venules where an Arthus-type reaction occurs resulting in vasculitis and tissue damage. Examples are gastrointestinal bleeding, gastroenteropathy, and chronic pulmonary disease. Finally, type IV or delayed hypersensitivity reactions are mediated by T-cells and are exemplified by contact dermatitis. It also may be involved in the pathogenesis of gastroenteropathy and chronic pulmonary disease. More than one mechanism may be involved in any par-

*Author to whom all correspondence and reprint requests should be addressed.

Table 1
Common Manifestations of Food Allergy in Infants

Gastrointestinal
Vomiting
Diarrhea
Abdominal pain
Intestinal bleeding
Constipation
Eosinophilic gastroenteritis
Protein-losing enteropathy
Dermatologic
Atopic dermatitis
Urticaria
Angioedema
Contact rash
Respiratory
Rhinitis
Cough
Wheeze
Chronic pulmonary disease (Heiner's syndrome)
Otitis Media
Other
Systemic anaphylaxis
Anemia
Thrombocytopenia
Proteinuria
Irritability/sleeplessness
Failure to thrive

ticular subject or manifestation, which may explain the variation in presentation and the difficulty in diagnosis.

Epidemiology

Reported frequencies of various manifestations of food allergy in infants varied widely. This is the result of differences in study design, population studied, case selection, diagnostic criteria, and investigator's attitude about the spectrum of manifestations. Prospective studies of unselected birth cohorts (2,3) showed that food-allergic children often have multiple symptomatology that involve different shock organs. The gastrointestinal tract and the skin are the most frequently involved systems, followed by the respiratory system and then other body systems.

The prevalence of food allergy peaks during the 1st yr of life and the onset of symptoms usually occurs during the first 6 mo (4). This trend may be explained partly by the relative enzymatic and immunologic immaturity of the gut, which in turn increases the susceptibility

of genetically allergy-prone infants to food hypersensitivity. Earlier reported incidence of cow's milk allergy varied from 0.3–10% (5–7). More recently, Host and Halcken (2) prospectively studied 1749 unselected Danish newborns and found the prevalence of cow's milk allergy to be 2.2% based on elimination/open milk challenge procedures. In the United States, Bock (8) followed 480 children from birth until their 3rd yr of life and reported 8% of the children to have food allergy confirmed by oral food challenge.

Although any food can potentially produce an immunologic adverse reaction, only few foods account for the vast majority of cases in children. Most commonly implicated is milk, followed by eggs, soy, wheat, and peanuts. The quantity and frequency of ingestion of a particular food, together with its intrinsic allergenicity, influence the likelihood of a particular food to be a significant allergen. However, in exquisitely sensitive subjects, minute quantities of the offending food may cause life-threatening reactions. So far, there is no evidence that the specific food allergen is genetically determined (9,10).

Since the medical history, allergy skin testing, and/or in vitro tests by themselves are rarely definitive of food allergy diagnosis, an oral challenge test is usually needed to confirm the diagnosis (11). Oral food challenges are best conducted in a blind fashion, although open challenges can be reliable in infants and young children (12). The following review on clinical manifestations of food allergy in infants is mostly based on studies that used food challenge in confirming the diagnosis.

Gastrointestinal Manifestations

The gastrointestinal tract is the major shock organ in food allergy in infants, exhibiting more than one-half (50–60%) of the presenting symptoms (2,3). The gut is a major immunologic organ that is uniquely adapted in allowing passage of nutrient proteins (oral tolerance) but at the same time protecting the body from harmful luminal pathogens ("mucosal barrier" function) (13). Failure of development, or a breakdown, of oral tolerance is believed to enhance the development of food hypersensitivity.

Vomiting

Vomiting accounts for 12–50% of presenting symptoms (3,4). It usually occurs within minutes to 1 h of food ingestion and may be mild, presenting as spitting, or severe and projectile, that may lead to dehydration and electrolyte imbalance.

The character of the vomitus varies. It usually contains mucus but also can be bile stained or blood streaked. In a minority of patients where vomiting is the predominant symptom, severe antral gastritis,

with or without small bowel involvement, has been seen (14). In the majority of cases, vomiting is associated or followed by other gastrointestinal symptoms, particularly colic and diarrhea.

Diarrhea

Diarrhea of various degrees is the presenting symptom in one-fourth to one-half of food-allergic children (4). Stools of food-induced diarrhea do not seem to have distinct characteristics. They often contain visible mucus and may be blood streaked. Some patients may have persistent or severe diarrhea, which may be associated with dehydration, electrolyte imbalance, malabsorption, and weight loss. In such cases, secondary intolerances to lactose and other foods often exist depending on the degree of intestinal mucosal damage. The onset of diarrhea is usually rapid, occurring within 30 min to a few hours of food ingestion (3).

In the rapid-onset diarrhea, an immediate type hypersensitivity is the most likely etiology. Mice that were parenterally passively immunized with monoclonal IgE antibodies to bovine β -lactoglobulin (BLG) developed immediate hypersensitivity to orally ingested bovine BLG (15). At 30 min after the challenge feed, fluid accumulation, increased gut permeability, and edema of the small intestinal villi were noted. This acute reaction is associated with functional changes in the epithelial fluid and electrolyte transport, but without substantial histological changes (16).

In some cases however, the onset of diarrhea may be delayed, making it difficult to attribute symptoms to specific food hypersensitivity, particularly since allergy skin testing is usually negative in such cases (17). Hill et al. (18) also identified a group of late reactors (onset >20 h from the start of food challenge) who had symptoms of chronic diarrhea along with chronic respiratory and eczematous reactions. Positive radioallergosorbent test (RAST) and skin-test reactions were confined to those presenting with eczematous lesions.

Abdominal Pain

Abdominal pain in the form of colic or diffuse stomach ache may be encountered in about one-fourth to one-half of food-sensitive children (4). In early infancy, the pain seems to be caused by colic, characterized by bouts of excessive crying usually lasting for 2–3 h. The abdomen is tense and the legs are characteristically drawn up. The attack may terminate only when the infant is completely exhausted or when there is passage of stools or flatus.

It is worth noting that colic is not a well-defined symptom and may result from numerous factors that in many cases cannot be identified. Probably about 10% of colic can be attributed to food allergy. In a double-blind crossover study of 24 infants with severe colic, the symp-

tom was reproduced in 18 infants who were given whey protein compared to only 2 infants who were given placebo (19). This study should not imply a high rate of food-induced colic since these infants were preselected according to their improvement on a cow's milk-free diet. The colic in these infants was also more severe and unresponsive to the usual intervention measures.

Colic in exclusively breast-fed infants is significantly less frequent than formula-fed infants and is often related to foods ingested by the mother and excreted in her milk (20–22).

Intestinal Bleeding

Food-induced gastrointestinal bleeding may be manifested as visibly bloody stools or more commonly as nonvisible occult bleeding. Occult bleeding is a low-grade blood loss that usually occurs in infants and may persist for prolonged durations, resulting in iron deficiency anemia despite adequate dietary intake of iron (23). Wilson and coworkers (24) noted occult bleeding in 40% and the presence of circulating precipitating antibodies to cow's milk in >75% of those anemic infants. Fecal blood loss, quantitatively determined by ^{51}Cr -labeled autologous erythrocytes, varied from 0.6–10.3 mL of blood per day depending on the amount of cow's milk ingested. The sera of these infants contained high titers of precipitating antibodies mostly to the heat-labile bovine milk protein fractions serum albumin and serum globulin. On elimination of homogenized cow's milk and substitution with heat-treated milk or soy formula, a profound decrease in blood loss was noted. Follow-up of several of these infants revealed that milk-induced bleeding seldom persists beyond the age of 2 yr (25).

Gross bleeding is less common. It was noted in 10% of 54 milk-allergic children (26). In a recent prospective study of unselected birth cohorts in Denmark, there were no reported cases of gross bleeding among the milk-allergic children (4). Hematochezia may result from a variety of disorders. Only in some cases will it be the result of food hypersensitivity. Food-induced colitis is typically seen in infants 3–10 mo old, with loose stools containing excessive mucus and blood. Severe diarrhea is, however, rare (27). Peripheral and/or stool eosinophilia frequently exist. On colonoscopy, the rectosigmoid area appears to be the most commonly affected region, with characteristic superficial mucosal aphthoid ulcerations with intervening normal mucosa. In a selected group of infants, Berezin et al. (27) identified 22 infants (age 2–16 wk) presenting with hematochezia who had positive milk challenges. One half of these infants were on cow's milk formula while the rest were either on breast milk, soy formula, or mixed feedings. Cow's milk elimination from the diet of the infants and of their lactating mothers resulted in resolution of hematochezia within 1–2 wk.

Constipation

Although it is conceivable that diarrhea can result from intestinal food hypersensitivity, constipation may be the manifestation in some subjects (28). The condition seems to be more common in infants and young children and manifest as painful passage of hard stools once every several days. The condition may be recalcitrant to the usual stool softeners and laxatives. In one study, approx 5% of children with cow's milk allergy presented with constipation (29). In a recent study (30) of 27 consecutive children referred for chronic constipation, 21 showed improvement on cow's milk elimination. There was a return of normal stools within a few days with resolution of abdominal pain, perianal fissures, and erythematous edema of the anus. Milk challenge induced constipation within 48 h. Four of these subjects had other associated symptoms of milk allergy, but 15 of 27 had a past history of cow' milk allergy.

Eosinophilic Gastroenteritis (EG)

This is a relatively rare disorder characterized by peripheral eosinophilia; eosinophilic infiltration of the bowel wall; and various gastrointestinal symptoms, primarily pain, vomiting, and diarrhea with or without occult bleeding. The underlying mechanism is not clear and the condition affects adults more often than children (31). In about one-half of patients, there are atopic manifestations, increased serum total IgE, and positive RAST to specific foods, all of which support an IgE-mediated mechanism.

The manifestations of EG depend on the area and depth of maximal gastrointestinal involvement. Children with mucosal involvement usually present with vomiting, watery diarrhea with or without blood, iron deficiency anemia, abdominal pain, and failure to thrive. Those with predominantly muscular involvement may mimic gastroesophageal reflux or gastric outlet obstruction such as pyloric stenosis (32). Regurgitation, blood-streaked or bilious vomiting, and weight loss are frequent. Those with subserosal involvement, however, manifest predominantly with ascites along with abdominal distention, vomiting, and diarrhea (31). Symptoms usually begin to improve within days of elimination of the incriminated food allergen, and spontaneous resolution usually occurs by 2–3 yr of age (33). Fatal cases resulting from bowel perforation have been reported, but are rare (34).

Protein-Losing Enteropathy

Waldmann et al. (35) described a form of milk-induced gastroenteropathy which is associated with severe hypoalbuminemia, anemia, edema, and failure to thrive. The syndrome has some overlapping

features with EG, particularly regarding the presence of increased eosinophils in the circulation, intestinal mucosa, and stools. Such patients usually have increased serum milk precipitins, implying a type III hypersensitivity reaction (immune complexes) as the underlying mechanism. The increased gastrointestinal protein loss can be demonstrated using radioisotope-tagged albumin. Elimination of milk in the diet or corticosteroid therapy results in a striking decrease of intestinal protein loss.

Although most cases of protein-losing enteropathy are caused by cow's milk, other foods, such as soybean formula, have been incriminated (36). Recently, casein hydrolysate formulas have been implicated in a child with allergic enterocolitis that responded only to an elemental diet (37).

Dermatologic Manifestations

The role of food in cutaneous allergy, particularly atopic dermatitis (AD), has been increasingly appreciated in recent years as a result of several well-controlled studies that showed cutaneous reactions as one of the most common manifestations of food allergy. Recent prospective studies of unselected birth cohorts reveal that cutaneous manifestations occur in about one-half (30–64%) of challenge-proven food-sensitive children (3,4).

Atopic Dermatitis

AD is a chronic inflammatory skin disorder which usually has its onset during infancy (38). It is estimated that about 10% of infants are affected by AD (39). In the acute and subacute stage, the disease is characterized by intensely pruritic and erythematous papulovesicular lesions that may weep and crust. Intense pruritus induces rubbing and scratching which in turn result in excoriations and often bleeding. In chronic cases, marked dryness, scaly lichenification, and excoriated fibrotic papules are seen. The distribution of the skin lesions vary with age. In infants, it typically appears on the cheeks, scalp, and behind the ears, and later affects the neck, trunk, and extensor surfaces of the extremities. In late childhood, the flexor surfaces become the most affected.

AD is a multifactorial disease with underlying skin abnormalities, local and systemic immunologic dysregulation, and multiple exacerbating factors (40). Several studies have shown a substantial role of food allergy in infantile AD. Burks and coworkers (41) found 33% of children with mild to severe AD to have challenge-proven food allergy. Sampson (42) reported a higher frequency of 63% that may be attributed, at least partly, to differences in the study population. In a pro-

spective study of unselected birth cohort, eczema occurred in one-half of the challenge-proven milk-allergic children (4).

In infants at high risk of atopy, formula feeding and early introduction of solid foods were associated with a high incidence of AD (43–46). In such cases, AD may appear as early as a few weeks of age. Exclusively breast-fed infants, however, may develop AD caused by foods ingested by the mother and excreted in her milk (47,48).

Several findings point to a major role of IgE-mediated reactions in AD. Total serum IgE level is highly elevated in most patients and correlates with the extent and severity of lesions. Increased skin reactivity and serum IgE-antibody levels to foods and other allergens frequently exist. However, many of these suspected allergens are not clinically relevant as shown by food challenges (49).

During food challenge, skin manifestations characterized by pruritic erythematous macular or morbilliform rash are observed between 5 min and 2 h of initiation of food challenge (42). Symptoms confined to the skin occurred in only 30% of the patients and a majority had associated gastrointestinal and respiratory symptoms. Positive food challenges are usually associated with the sharp increase of plasma histamine level in the absence of circulating basophil activation or the presence of complement activation products such as anaphylatoxins C3a and C5a (50,51). The late phase of the IgE-mediated response also has been observed with a second skin reaction noted approx 4–8 h after the onset of the primary skin reaction. An increase of circulating polymorphonuclear leukocytes was observed along with skin lesion biopsies revealing eosinophilic infiltration and deposition of major basic protein in the upper dermis (51). It is noteworthy that in some patients, T-cell dysfunction and cytokine production abnormalities have a greater role than IgE (40,52,53).

Urticaria/Angioedema

Urticaria results from sudden histamine release in the skin with subsequent vasodilation, erythema, wheal formation, and intense pruritus. Acute urticaria usually disappears within hours to a few days, but new waves of lesions may appear. Urticaria that persist for more than 6 wk is generally considered "chronic."

Foods, and to a lesser extent food additives, are among the common causes of acute urticaria. Among challenge-proven milk-allergic infants, urticaria/angioedema occurred in 10–15% of the cases (2,18). During food challenge, urticarial lesions are usually reproduced within a few minutes of food ingestion. In fact, in some patients, mere skin or mucous membrane contact with food may cause localized or generalized urticaria or angioedema. Food allergy is rarely implicated in chronic urticaria, unless the offending food is eaten almost daily.

Contact Rash

Food-induced contact rashes have been observed in some infants (54,55). The rash is usually in the form of blotchy erythema and occasionally urticarial. In infants, these usually involve the perioral areas, chin, neck, and upper part of the chest. The rash generally disappears within a few hours if there is no further contact with the offending food. In some infants, the rash is perianal as a result of contact with the fecal food residue.

Respiratory Manifestations

The role of food hypersensitivity in causing respiratory symptoms is probably markedly underestimated (56). Prospective studies (2,3) showed that 20–33% of milk-allergic infants presented with respiratory symptoms, either alone or more often in association with other allergic manifestations, especially AD. Chronic respiratory symptoms noted early in life, especially in association with other atopic manifestations and a high-serum IgE, should be suspected of having a food hypersensitivity.

Rhinitis

Chronic rhinitis, characterized by nasal stuffiness, persistent watery or mucoid rhinorrhea, and sneezing, occur in 5–20% of milk-allergic infants (2,3). The mechanism involved is probably that of an IgE-mediated reaction from ingestion and possibly inhalation of food allergens. The onset of rhinitis may occur within minutes to 2 h after initiation of food challenge (57) or as late as 20 h or more following food ingestion (54). The delayed onset of these symptoms makes it difficult to suspect food hypersensitivity as a cause. One-half of the delayed reactors presented with chronic rhinitis, coughing, and wheezing along with chronic diarrhea, eczema, and failure to thrive.

Cough/Wheeze

In two prospective studies (2,3), about one-third of milk-sensitive infants presented with wheezing. In a series of 32 young children with asthma and suspected milk allergy, wheezing was reproduced by milk challenge in 10 (31%) (58). The condition was more likely to be associated with early age, elevated IgE levels, and positive skin test to milk proteins. On the other hand, in a series of 20 food-allergic subjects, mostly older children who had asthma and other allergy manifestations, asthma was reproduced by food challenge in only 2 subjects, excluding 3 who had systemic anaphylaxis (59). Other workers noted that <5% of milk-sensitive infants exhibited respiratory symptoms as the sole manifestation of milk allergy (17,18). As with rhinitis, food-

induced coughing and wheezing can occur within minutes or after 20 h (54). In late reactors, the role of milk allergy is often unrecognized since the onset is insidious and the symptoms appear unrelated to milk ingestion. Symptomatic pharmacologic treatment of these infants rarely brings complete relief until milk is eliminated from the diet.

Milk-Induced Chronic Pulmonary Disease (Heiner's Syndrome)

This is a relatively rare disorder that was initially described by Heiner and Sears in 1960 (60). The originally described group of seven children had an age range of 6 wk to 15 mo. Typically, these infants are fed cow's milk and present with chronic coughing and wheezing, and sometimes hemoptysis. The chest roentgenogram may show persistent or recurrent patchy infiltrates, usually bilateral. Other radiologic findings include atelectasis or consolidation, reticular densities, pleural thickening, and sometimes hilar adenopathy. The infiltrates are predominantly an Arthus-type reaction from immune complex deposition. The serum contains high titers of precipitating antibodies (mostly of the IgG isotype) to multiple cow's milk protein fractions (61). IgE antibodies are probably not involved or may only have a secondary role. Associated symptoms can be chronic rhinitis, otitis media, gastrointestinal symptoms, anorexia, failure to thrive, anemia, and eosinophilia.

In some patients with this syndrome, vasculitis may be severe enough to cause bleeding in the alveolar capillaries and result in pulmonary hemosiderosis (62). Hemoptysis with hypochromic microcytic anemia may be prominent. The diagnosis can be verified by demonstration of iron-laden macrophages in smears of tracheal aspirates (or morning gastric washings) stained with Prussian blue.

The symptoms usually improve within days after avoidance of milk, but the pulmonary infiltrate on chest roentgenograms may not resolve until several weeks. Recurrence of symptoms may also not occur until several days after milk challenge. Aspiration of milk possibly could have a role in this disease (63). Aspiration alone, however, cannot explain the whole syndrome.

Otitis Media

The role of allergy, especially that to food, in middle ear disease is controversial. To date, there are still no well-controlled studies that have found a correlation between food allergy and otitis media with effusion (OME). A control population is particularly important in studies on such a disease since OME can completely resolve spontaneously, with or without medical treatment (64). Also, many children with chronic otitis media have no symptoms or history of allergy. In a series of 200 randomly selected children with OME, 24% had inhalant allergy,

but food allergy did not appear to have a significant role (65). A higher prevalence of allergy (35%) was noted in a subgroup that had multiple tympanostomy tube insertions. Studies aimed at demonstrating the middle ear as a target organ for allergy has shown inconsistent findings. It seems that IgE plays a role in a subgroup of such patients. In one study (66), only 8% of 100 children with recurrent OME exhibited an elevated IgE in the middle ear effusion. The same authors (67) noted that in otitis-prone children, food-specific IgG antibodies and IgG-antigen immune complexes in both the serum and middle ear were higher than in controls.

Eustachian tube dysfunction (ETD) may contribute to the development of OME. Young infants, compared to older children and adults, have significantly less ability to equilibrate a negative ear canal pressure and may be prone to more prolonged episodes of ETD from repeated allergen exposure (68). Recently, Nsouli et al. (69) reported that 66 of 104 children (age 1.5–9 yr) with recurrent serous otitis media developed a recurrence of OME after elimination/open food challenge procedure. Although blind-challenge testing was not used to confirm the relationship and there was no control group, these findings suggest that food hypersensitivity has a role in a subgroup of children with recurrent OME, albeit at a much lower frequency than being implied by that study.

Systemic Anaphylaxis

Systemic anaphylaxis is an uncommon but potentially fatal manifestation of food allergy in exquisitely sensitive infants. It usually develops within a few minutes to a half hour of ingestion of even small quantities of food. Early symptoms may include itching, abdominal cramping, vomiting, urticaria, angioedema, stridor, shortness of breath, and wheezing. This may rapidly progress to hypotension, cardiac dysrhythmias, and vascular collapse. In a recent case report (70) of egg anaphylaxis in a 6-mo-old infant, the presentation mimicked foreign body aspiration.

Anaphylactic reactions to food seem to be almost always IgE mediated. In most of these patients, the reaction has occurred more than once and the relationship to food intake is usually so obvious as to warrant against verification with an oral food challenge or even skin testing, definitely not by the intradermal technique. RAST is much preferred.

Anaphylaxis in exquisitely sensitive infants may develop from very minute quantities of food. Jarmoc and Primack (71) reported the case of a milk-sensitive child who developed systemic anaphylaxis on two occasions, witnessed by physicians, immediately after the applica-

tion of a diaper rash ointment (Diaperene) that contained 5% calcium caseinate. Anaphylaxis has also been reported in a breast-fed infant to cow's milk excreted in the mother's milk, and in whom inadvertent milk challenges, including one with a casein hydrolysate formula, resulted in three episodes of anaphylactic shock (72). We (73) reported a case of a milk-sensitive boy who at 3 yr of age was subjected to a very cautious challenge supervised by an allergist, yet he developed explosive anaphylaxis immediately following the ingestion of a sip of casein hydrolysate formula that was diluted 1:4. In such cases, the importance of strict avoidance of the offending food and the emergency administration of epinephrine cannot be overemphasized.

Miscellaneous

This section briefly deals with a group of manifestations that are rare, controversial, or not well described.

Anemia

The association between whole cow's milk ingestion, gastrointestinal blood loss, and iron deficiency anemia has been recognized for many years. The anemia can be severe (hemoglobin 3.7–8.9 g%) as to warrant blood transfusions (74). In a series of infants with iron-deficiency anemia, one-half developed increased fecal blood loss on challenge with whole cow's milk (25). Precipitating antibodies to the heat-labile fractions of milk were noted in the majority of the anemic subjects. Substitution with soy- or a heat-processed formula resulted in a significant decrease in fecal blood loss and increase in hemoglobin. Ziegler et al. (75) noted that "HemoQuant" test, which is highly sensitive for detecting fecal hemoglobin, was positive in normal infants and that feeding homogenized milk increased the fecal blood loss in 38% of the children compared to only 4% in those who were fed milk formula. Hypochromic microcytic anemia was also commonly observed in children with milk-induced chronic pulmonary disease, especially if it was severe enough to lead to pulmonary hemosiderosis (62).

In most children, however, anemia is a result of the low content and poor bioavailability of iron in cow's milk (76). Feeding with iron-fortified formula showed no such adverse effects (77) and may account for the low frequency of anemia noted today.

Thrombocytopenia

A small number of studies reported that food allergy may cause various degrees of thrombocytopenia. Osvath and Markus (78) studied hematologic changes before and 3 h after food challenge in 35 children with milk and egg allergies. In 80% of the subjects, the platelet count

was reduced by >35%, and the eosinophil count increased more than twofold from baseline.

Severe thrombocytopenia and purpura was well documented in a newborn infant that remarkably improved following discontinuation of the milk formula, only to recur with reintroduction of that formula (79). Some patients with thrombocytopenia and absent radius syndrome also seemed to show improvement in their platelet counts with cow's milk elimination (80).

Proteinuria

Aggravation or precipitation of proteinuria has been attributed to food hypersensitivity in a few patients. Sandberg et al. (81) reported six children with steroid-responsive nephrotic syndrome who improved solely on milk-free diet when they had a disease relapse. Cow's milk challenge induced significant proteinuria, edema, and oliguria, and remission occurred within 3–10 d of milk elimination.

Recently, Sieniawska and coworkers (82) reported improvement of proteinuria after 3–8 d of milk-free diet in 6 of 17 children with steroid-resistant nephrotic syndrome. Proteinuria relapsed several days after reintroduction of milk. The group of responders to milk-free diet were characterized by a relatively younger age (mean age 1.6 yr), early feeding with cow's milk, and coexistence of allergic symptoms. However, milk-free diet was not beneficial in any of the cases with focal and segmental glomerulosclerosis. Two of the six children tolerated milk after more than a year in remission on a milk-free diet. It seems that cellular mechanisms may have a role in milk-induced steroid-resistant nephrotic syndrome as evidenced by the late-onset clinical reaction to milk challenge, positive lymphocyte migration inhibition tests, absent milk-specific IgE antibodies, and negative skin test to milk.

Irritability/Sleeplessness

Classic allergic manifestations to food in children are frequently associated with irritability. In a large series of milk-allergic children, irritability was noted in 40%, which disappeared on milk elimination and recurred following challenge (54). It is not clear whether that irritability was a primary central nervous system reaction or was secondary to the associated allergic manifestations.

A few studies suggested that persistent sleeplessness in certain infants may be related to food hypersensitivity. Kahn et al. (83) studied eight infants (age 7–46 wk) with marked sleeplessness and suspected milk allergy. On feeding with a hydrolysate formula, the authors documented in the sleep laboratory an increase in the sleep time per 24 h from 4.5 to 10 h and a decrease in the number of awakenings per night from five times to only occasional episodes. Because of the possible

inclusion of infants with sleeplessness due to colic, the same group of authors (84) later followed 17 children (2.5–29 mo old) for 24 mo. In all but one child, the sleep parameters, as documented in the sleep laboratory, significantly improved within 4–6 wk of milk-exclusion diet. The median sleep duration per 24 h increased from 5.5 to 9 h. There was also a decrease in the median number of awakenings per night from five to one, and in the length of awakening time from 32 to 14 min. Double-blind milk challenge induced recurrence of insomnia and agitated behavior.

Failure to Thrive

Poor growth may be seen in children with food allergy, particularly when the shock organ is the gastrointestinal tract and there is anorexia, vomiting, diarrhea, malabsorption, exudative enteropathy, or bleeding. Several studies showed that failure to thrive may be present in 10–20% of milk-allergic children (2,85).

Prognosis

The prognosis of food allergy in infants is generally good, particularly with strict avoidance of the offending foods. Prospective studies of unselected children revealed that approximately one-half became tolerant to milk by 1 yr of age, three-fourths at 2 yr, and almost all (80–90%) by 3 yr (2,8,85). In a series of milk-sensitive children, milk tolerance was noted in one-third by 2 yr of age, in one-half by 4 yr, and in three-fourths by 6 yr (86). In food-sensitive AD children, Sampson and Scanlon (87) observed clinical tolerance in one-third after 1–2 yr of avoidance of the implicated food. Followup of nine severely allergic children after 3–9 yr of avoidance of the offending food revealed that three were able to tolerate normal amounts of the food, four could tolerate small amounts, and only two continued to have clinical reactivity (88).

Some studies showed that positivity of skin test and/or RAST often persist longer than clinical reactivity (87,88). However, Hill and coworkers (89) noted that children who achieved clinical tolerance tended to have a significant decrease in skin-test reactivity and that those with a high-specific IgE-antibody titers had a more persistent clinical reactivity. Likewise, Host and Halken (2) noted that loss of clinical milk reactivity was significantly higher in infants with non-IgE mediated reactions (negative skin test and RAST).

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