
Case report

Acrodermatitis enteropathica–like eruption and food allergy

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Background: Acrodermatitis enteropathica–like eruption (AE) is a distinct rash associated with profound zinc deficiency. It is seen in a variety of conditions but has not been reported as a presentation of food allergy.

Objective: To report AE as an unusual presentation of food allergy in infants.

Methods: Acrodermatitis enteropathica–like eruption was diagnosed by a characteristic rash and a low serum zinc level. The diagnosis of food allergy was made by history, serum total IgE and food specific IgE levels, or oral challenge with suspected foods.

Results: Two infants with AE, diarrhea, and low serum zinc levels were evaluated. Food allergy was found in both infants. The first infant had a serum IgE level of 4,642 IU/mL. Specific IgE levels to milk, soybean, wheat, and peanut were 39.04, 10.14, 5.65, and 102.61 kU/L, respectively. Oral challenges to milk and peanut were positive and to soybean were negative. The second infant had a serum IgE level of 991 IU/mL; specific IgE levels to soybean and milk were 36.9 and 0.53 kU/L, respectively. Evaluation for other possible causes of diarrhea revealed homozygous delta F508 in the first infant, confirming the coexistence of cystic fibrosis; findings in the second infant were negative.

Conclusions: Undiagnosed food allergy can lead to profound zinc deficiency. Food allergy should be suspected in a child with acquired AE.

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INTRODUCTION

Food allergy is a common adverse immunologic response to food that occurs in up to 8% of children.¹ The skin and gastrointestinal tract are the most frequently targeted organs. Dermatologic manifestation of food allergy is frequently due to a direct immune-mediated reaction to the skin, which can lead to several manifestations, including acute urticaria, angioedema, atopic dermatitis, and dermatitis herpetiformis. On the other hand, acrodermatitis enteropathica–like eruption (AE) is a rare, acquired, nonimmunologic skin condition that occurs as a consequence of profound zinc deficiency associated with a variety of conditions, including malnutrition, cystic fibrosis (CF), anorexia nervosa, total parenteral nutrition without supplementation of zinc, and breastfeeding.² We describe 2 infants with AE caused by severe food allergy.

CASE REPORTS

Case 1

A 5-month-old full-term white boy had a 6-week history of diarrhea, failure to thrive, and worsening of a generalized

rash. The diarrhea was characterized by a moderate amount of loose to seedy bright green bowel movements 6 to 8 times per day that started at about the same time as the rash first appeared. A erythematous and maculopapular rash started around the perineum area and the posterior aspect of both thighs, gradually spreading over the entire body in 7 to 10 days. The rash then became scaly and flaky and was surrounded by a sharp border. The infant was not responsive to topical treatment with corticosteroids or antibiotics. He was exclusively breastfed, with excellent intake and appropriate urination. There was no history of emesis. Family history revealed asthma in the maternal uncle. There was no family history of food allergy, immunodeficiency, or any inherited disorders. Pertinent physical examination revealed the following: weight, 5.78 kg (3rd percentile); height, 63 cm (25th percentile); and head circumference, 42 cm (25th percentile). He was afebrile and irritable. There was generalized, nonpitting edema and a generalized rash characterized by erythematous, scaly, sharply demarcated psoriasiform. The rash covered the entire body but predominantly the perianal and perioral areas (Fig 1). There was no mucous membrane involvement. Respiratory, cardiovascular, abdominal, and neurologic examination findings were unremarkable. Laboratory findings revealed anemia, hypoproteinemia, and hypoalbuminemia (Table 1). The patient's serum zinc level was 40 $\mu\text{g/dL}$ (reference range, 66–110 $\mu\text{g/dL}$), and the zinc level in the mother's breast milk was 330 $\mu\text{g/dL}$ (reference range,

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Figure 1. Generalized, erythematous, scaly, sharply demarcated, psoriasiform rash in the first infant.

17–302 $\mu\text{g}/\text{dL}$). Oral administration of elemental zinc in the form of zinc sulfate, 2 mg/kg per day, led to improvement in the rash within a couple of days. He was discharged from the hospital with zinc supplementation and was instructed to attend outpatient follow-up. However, the patient returned 10 days later with worsening of the rash. Zinc supplement therapy was given only for a few days after hospital discharge owing to lack of compliance.

A punch skin biopsy specimen taken from the right anterior thigh revealed interface dermatitis with parakeratosis and focal pustulosis of the stratum corneum consistent with nutritional dermatosis and AE. Immunofluorescence staining revealed the absence of immunoglobulin and complement deposition. Findings from initial evaluations for other causes of diarrhea were negative. Further laboratory results revealed an elevated serum IgE level (4,642 IU/mL; reference range, <12 IU/mL), and specific IgE levels to milk and peanut by fluoroenzyme immunoassay (CAP-FEIA; Pharmacia, Uppsala, Sweden) were elevated (Table 1). A diagnosis of food allergy was made, and breastfeeding was discontinued. An amino acid–based formula (Neocate; SHS North America, Gaithersburg, MD) and zinc supplementation were initiated.

Moisturizer cream was applied to the entire body, and 1% hydrocortisone cream was applied on the trunk and extremities but not on the face. A bandage was used to restrain the patient from scratching in the first few days of hospitalization. Rash and diarrhea were completely resolved after 1 week.

Two weeks later, genetic results revealed homozygosity for the delta F508 mutation, which confirmed a diagnosis of CF. Pancreatic enzyme supplementation was initiated. Zinc supplementation was continued for 2 months and then discontinued. The serum zinc level in the patient remained normal.

The infant underwent graded oral challenge to milk, soy, and peanut after 6 weeks of being asymptomatic and avoiding certain foods. The milk challenge was performed with an initial dose of 2.5 mL of cow's milk–based formula, with double the amount given every 20 minutes if no reaction was observed. The final dose was planned for 40 mL of formula (total dose, 77.5 mL). The patient developed wheezing, generalized urticaria, and vomiting within minutes of ingesting the initial dose. The following week the infant had a similar reaction to peanut challenge. However, he tolerated the oral challenge with soy formula (total dose, 105 mL) without any adverse reaction.

Table 1. Demographic and Laboratory Data for Infants With Acrodermatitis Enteropathica

Characteristic	Case 1	Case 2	Reference values	Decision value*
Age at onset	31/2 mo	3 wk	NA	NA
WBC count, $\times 10^3$ cells/ μ L	17,000	21,400	5–19.5	NA
Hemoglobin, g/dL	8.5	9.1	10.5–14.0	NA
Hematocrit, %	24.9	26.8	32–42	NA
Erythrocyte count, $\times 10^6$ cells/ μ L	3.2	2.79	3.8–5.4	NA
Mean corpuscular volume, fL	77.8	95.9	72–88	NA
Absolute eosinophil count, cells/ μ L	575	169	50–250	NA
Blood urea nitrogen, mg/mL	6	4	4–19	NA
Sodium, mEq/L	143	136	135–145	NA
Potassium, mEq/L	5.2	5.0	3.5–5.3	NA
Chloride, mEq/L	111	107	101–111	NA
Carbon dioxide, mEq/L	21.1	15.1	17–25	NA
Creatinine, mg/dL	0.4	0.4	0.3–0.5	NA
Albumin, g/dL	1.54	1.50	3.8–5.4	NA
Total protein, g/dL	3.02	3.60	4.4–7.6	NA
ALT, IU/L	67	21	13–45	NA
AST, IU/L	67	22	15–60	NA
Alkaline phosphatase, IU/L	277	154	110–302	NA
Serum zinc, μ g/dL	40	43	66–110	NA
Stool occult blood	Negative	Negative	Negative	NA
Stool leukocyte	No PMNs, no eosinophils	Few PMNs, no eosinophils	No PMNs, no eosinophils	NA
CF mutation analysis	Homozygous delta F508	Normal	Normal	NA
Serum IgE, IU/mL	4,642	991	<12	NA
Food specific IgE, kU/L				
Milk	39.04	0.53	<0.35	>15†
Soybean	10.14	36.9	<0.35	>30‡
Wheat	5.65	Not performed	<0.35	>26§
Peanut	102.61	Not performed	<0.35	>14†

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; NA, not applicable; PMNs, polymorphonuclear leukocytes; WBC, white blood cell.

* Data are based on double-blind, placebo-controlled food challenge.¹

† 95% positive predictive value.

‡ 73% positive predictive value and 94% specificity.

§ 74% positive predictive value and 92% specificity.

Case 2

A 5-week-old African American boy had a 2-week history of watery diarrhea, abdominal distention, and failure to gain weight. A red, scaly rash developed at 4 weeks of age. He was exclusively fed with soy formula from birth owing to parental concern because his older sibling had cow's milk intolerance. The patient was fed approximately 24 to 26 oz daily. Two days before hospital admission, because of diarrhea and dehydration, he was given an oral electrolyte maintenance solution. Review of systems revealed no fever, vomiting, or respiratory tract symptoms. The patient had poor weight gain since birth and acute weight loss of 250 g in 2 weeks before admission. He was born full term without complications, weighing 3.4 kg. Family history was negative for primary immunodeficiency or autoimmune diseases; a 3-year-old brother had vomiting and diarrhea from ingestion of cow's milk formula as an infant but can now tolerate milk. Initial examination revealed that the child was afebrile and tachycardic, with moderate dehydration. His weight was 3.08 kg. Weight, height, and head circumference were less

than the fifth percentile. A generalized coalescent, erythematous, scaling, psoriasiform rash covered his entire body, predominantly around the perioral and perianal regions. Other pertinent findings included mild abdominal distention, soft but not tender, and without hepatosplenomegaly. Neurologic examination results were not remarkable.

Laboratory findings included anemia, hypoalbuminemia, and low serum zinc levels (Table 1). Because of severe gastroenteritis and dehydration, total parenteral nutrition and zinc supplementation were initiated. Stool studies for leukocytes, Wright stain, reducing substance, and fecal fat; stool cultures for bacteria, virus, and fungus; and a stool test for rotavirus antigen were all within normal limits. Additional laboratory results included a serum IgE level of 991 IU/mL; specific IgE levels to soybean and milk were 36.9 and 0.53 kU/L, respectively (Table 1). Soy formula was switched to Neocate. After the third day of formula change, the rash was less erythematous, and developing desquamation started from the trunk to the extremities. The skin healed completely

without scarring or pigmentation within 7 days. Stool frequency decreased after 2 to 3 days. Upper and lower gastrointestinal endoscopy and biopsy, performed 1 week later, did not reveal any pathologic findings. An oral challenge with milk and soy formula was offered but declined by the parents.

DISCUSSION

Acrodermatitis enteropathica-like eruption is a term that describes a scaly, sharply demarcated, psoriasiform rash that predominantly involves periorificial and acral areas and that is associated with profound zinc deficiency ($<50 \mu\text{g/dL}$).² The characteristic rash, low zinc levels, and skin histology confirm the diagnosis of AE in our infant patients. Acrodermatitis enteropathica-like eruption has been reported in many acquired conditions, but this is the first report of food allergy presenting as AE.

The infants in this study were diagnosed as having food allergy based on a history of complete resolution of symptoms after food avoidance and elevation of total IgE and food specific IgE levels. Positive oral food challenge reactions to milk and peanut confirmed the diagnosis in the first infant. Food specific IgE by CAP-FEIA is accepted as a reliable test for the diagnosis of food allergy. It can be substituted for oral challenge with certain foods when the level of food specific IgE is greater than the recommended diagnostic value.¹ In the second infant, the specific IgE level to soy was elevated higher than the diagnostic value that correlates with a 73% positive predictive value and 94% specificity in predicting soy allergy. Extensive evaluation, including gastrointestinal endoscopy and biopsy, excluded other possible etiologies of diarrhea in this child.

Infants with CF have borderline low zinc levels due to malabsorption and abnormalities in zinc homeostasis.³ However, only a few cases of AE have been reported in infants with CF.⁴ This suggests that other contributing factors may be required for the profound zinc deficiency to develop. Although our first infant had coexisting CF, complete resolution of his symptoms after diet modification and zinc supplementation without pancreatic enzyme supplementation suggests the crucial role that food allergy plays. The AE in most infants with CF described previously^{4,5} improved after hypoallergenic formula or parenteral nutrition was given together with zinc and other supplements. However, a food allergy workup was not mentioned in those cases. Some of these infants with CF may have had unrecognized food allergies as a contributing factor to profound zinc deficiency.

Acrodermatitis enteropathica-like eruption can occur in breastfed infants whose mothers have low zinc concentrations in their breast milk.⁶ On the other hand, the high zinc level in our infant's maternal breast milk argues against this possibility. Maternal dietary protein can pass into breast milk during lactation within hours of food ingestion.⁷ In this report, it is possible that the first infant may have developed an allergic reaction to cow's milk or peanut allergens from the maternal breast milk.

Mutations in the *SLC39A4* or *SLC30A4* gene have been described in autosomal recessive, hereditary forms of AE.⁸ However, the fact that both infants discontinued zinc supple-

mentation after a few weeks without recurrence of symptoms and exhibited normal cell-mediated and humoral immune functions (data not shown) does not support the diagnosis of hereditary AE. The reason for anemia, hypoproteinemia, and low zinc levels in our infants is not clear. We postulate that they were consequences of sustained exposure to unrecognized allergic food protein, which led to IgE-mediated gastrointestinal symptoms and eventually malabsorption.

However, there are some limitations to this observation. First, breastfeeding or CF could have been a significant contributing factor to zinc deficiency in the first infant. Second, although convincing evidence supports the diagnosis of food allergy in these children, a double-blind, placebo-controlled food challenge, regarded as the gold standard for food allergy diagnosis, was not performed. Thus, additional well-designed studies may be required to confirm this observation. In conclusion, undiagnosed food allergy, with or without other confounding factors of zinc deficiency, can lead to profoundly low zinc levels and AE. Accordingly, food allergy should be recognized as a probable cause in a child with acquired AE.

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