Case in Point: Acrodermatitis Enteropathica

An Infant With Skin Lesions and Diarrhea From Zinc Deficiency

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A 10-month-old boy presented with a 2-month history of a recalcitrant diaper rash. Two weeks later, he developed lesions on the arms, legs, feet, and around the mouth. His mother noted that recently the infant was lethargic and irritable and had diarrhea in the past few days. The infant was born to a 24-year-old primigravida mother at term, following an uncomplicated pregnancy and vaginal delivery. The infant’s father was 30 years old and healthy. There was no history of consanguinity. The boy’s birth weight was 3.4 kg and his length was 52 cm. The neonatal course was uneventful. The infant was exclusively breastfed for the first 6 months and then weaned. Formula feeding and solid foods were introduced at 6 months. The family history was not significant for any similar problems.

Physical examination revealed erythematous well-defined plaques surrounded by hyperkeratotic rims in the perineal and perioral areas. The boy had multiple, similar lesions symmetrically distributed on his arms, legs, and feet, but his hair, nails, and mucosa were not affected. The rest of the physical examination was unremarkable.

Laboratory studies showed a serum zinc level of 32 µg/dL (reference range, 70-120 µg/dL) and alkaline phosphatase level of 60 U/L (reference range, 96-360 U/L). The complete blood cell count, serum albumin, lactate dehydrogenase, aspartate transaminase, and alanine transaminase were within reference range.

Based on the history, clinical appearance of the skin lesions, and the low serum zinc level, the infant was diagnosed as having acrodermatitis enteropathica. The patient was treated with oral elemental zinc supplementation at 3 mg/kg/day. The diarrhea subsided in 2 days, and the skin lesions resolved in 4 weeks.

DISCUSSION

Acrodermatitis enteropathica, which is caused by an inherited or acquired zinc deficiency, is characterized by the triad of acral and periorificial dermatitis, diarrhea, and alopecia. However, some authors prefer to use the term “acrodermatitis enteropathica” only for the inherited disease. The condition was first recognized by Brant in 1736; Danbolt and Closs coined the term in 1943.

PREVALENCE

Inherited acrodermatitis enteropathica occurs in 1 in 500,000 live births. There is no predilection for sex or race. Infants who are formula-fed typically show symptoms during the fourth to tenth week of life, whereas infants who are breastfed show symptoms days to weeks after weaning. This difference is because human breast milk contains a zinc transporter protein that potentiates zinc absorption, and there is increased bioavailability of zinc in breast milk. Premature infants are at particular risk and may show symptoms while breast-feeding.

Acquired zinc deficiency is more common than genetic forms. The prevalence is estimated at 1% to 3% in the United States and up to 20% in developing countries. Only individuals with moderate-to-severe acquired zinc deficiency manifest the disease.

ETIOPATHOGENESIS

Inherited acrodermatitis enteropathica is an autosomal recessive disorder with a mutation in SLC39A4, located on chromosome 8q24.3, that encodes the human zinc/iron-regulated transporter-like protein 4 (ZIP4) and plays an important role in zinc transmembrane transport and zinc uptake. This protein is highly expressed in the enterocytes in the duodenum and jejunum and is secreted in breast milk. Mutations of the gene may result in poor zinc absorption and subsequent deficiency.

Acquired zinc deficiency may result from zinc-deficient diets, total parental nutrition without zinc supplementation, conditions associated with decreased zinc absorption (eg, celiac disease, cystic fibrosis, inflammatory bowel disease, short-bowel syndrome, diet high in phytates), conditions...
associated with increased zinc demands (eg, prematurity, extensive burns), conditions associated with excessive zinc excretion (eg, renal tubular dysfunction, excessive use of a diuretic), or a combination of these factors.\textsuperscript{7,9}

Zinc has 3 vital metabolic functions, namely, structural, catalytic, and regulatory. It is an essential trace element and is vital to human growth and development.\textsuperscript{3,9} As a result, a moderate-to-severe deficiency in zinc will lead to abnormal intracellular zinc regulation, decreased synthesis and function of enzymes dependent on zinc, and loss of epidermal Langerhans cells with resultant clinical features of acrodermatitis enteropathica.\textsuperscript{7}

### HISTOPATHOLOGY
Histologic findings are nonspecific and include confluent parakeratosis, reduced granular layer, acanthosis, intracellular edema, spongiosis, and perivascular lymphocytic infiltrate. In late lesions, psoriasiform hyperplasia of the epidermis is often noted.\textsuperscript{4}

### CLINICAL MANIFESTATIONS
Early clinical findings of acrodermatitis enteropathica include perineal, perioral, and acral dermatitis.\textsuperscript{2} Classically, cutaneous lesions present with symmetrical, well-demarcated, erythematous, scaly, crusted, and variably
eroded plaques.8 The eruptions may appear eczematous, psoriasiform, and, less commonly, vesiculobullous.2,4 Erosions and pustules may develop.4 Alopecia, diarrhea, and failure to thrive may be present with more advanced cases. Infants affected by acrodermatitis enteropathica are often irritable, inconsolable, anorexic, emotionally labile, and apathetic.9 Other clinical findings include glossitis, stomatitis, hypogeusia, angular cheilitis, photophobia, decreased visual acuity, punctate keratopathy, Beau lines on the nails, onycholysis, and onychodystrophy.7,8

**DIAGNOSIS AND LABORATORY INVESTIGATIONS**

The diagnosis is mainly clinical based on the history and typical clinical features, especially if there is a family history of inherited acrodermatitis enteropathica. The diagnosis can be confirmed by demonstrating a low serum zinc level. Serum albumin should also be measured, as approximately 70% of zinc in the serum is bound to albumin, and zinc levels will be falsely low in hypoalbuminemia states. Serum alkaline phosphatase, a zinc-dependent metalloenzyme, is often decreased in affected individuals.7 It is important to check the serum alkaline phosphatase level, as this is the first indicator of zinc deficiency. Molecular genetic testing for a defect in the SLC39A4 gene is only available in some academic centers.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnosis includes cow’s milk protein allergy, candidiasis, intertrigo, seborrheic dermatitis, biotin deficiency, riboflavin deficiency, essential fatty acid deficiency, propionic acidemia, methylmalonic acidemia, Hartnup disease, kwashiorkor, psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, staphylococcal scaled skin syndrome, Wiskott-Aldrich syndrome, and epidermolysis bullosa.7,9,13-15

**COMPLICATIONS**

Affected individuals have impaired immune function and are susceptible to infection. Paronychia, blepharitis, and conjunctivitis may occur. Skin lesions may be secondarily infected with bacteria such as *Staphylococcus aureus*. Cutaneous candidiasis is particularly common in the eroded diaper area.7 Delayed wound healing, delayed puberty, hypogonadism, and altered mental status may also result from severe zinc deficiency.5,8

**PROGNOSIS**

Without treatment, the inherited disease is fatal. Affected individuals without treatment usually die within a few years. Currently, there is no cure for inherited acrodermatitis enteropathica. For the acquired form, the prognosis depends on the underlying cause.

**MANAGEMENT**

For inherited acrodermatitis enteropathica, treatment consists of supplementation of elemental zinc at a dose of 3 mg/kg/day.6,9 A high zinc intake is necessary because only a small fraction of zinc can be absorbed, without the aid of ZIP4. Lifelong supplementation is required,9 with possible dose increases during adolescence, pregnancy, and lactation. Serum zinc levels should be monitored periodically, and genetic counseling should be offered.

For the acquired form, supplementation with elemental zinc at a dose of 0.5 to 1 mg/kg/day is often required.9 The underlying cause should be treated if possible and zinc supplementation tapered as necessary. Proper skin care is essential in individuals with the condition, and consultation with a dermatologist is often warranted.

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**REFERENCES**


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