

Case report

Acrodermatitis enteropathica in three siblings

Arfan-ul-Bari, *Muhammad Abbas, *Simeen ber Rahman

PAF Hospital, Sargodha.

*Dermatology Department, Military Hospital, Rawalpindi

Abstract Acrodermatitis enteropathica is an autosomal recessive disease due to a partial disorder of intestinal zinc uptake. Signs usually appear within the first months of life, with a characteristic cutaneous rash that is symmetrical, located around the body orifices, behind the ears, and on hands, feet, and head. We report three siblings with characteristic features of the disease and laboratory evidence of low serum zinc levels. Symptoms in all three patients reversed remarkably on supplementation of zinc. A brief history, clinical profile, pathophysiology and treatment of the disease have also been discussed in this article for better understanding of this disorder.

Introduction

Acrodermatitis enteropathica (AE) was first described in 1942 by Danbolt and Closs. The condition is now recognized as an inborn error of zinc metabolism that is inherited as an autosomal recessive disorder.¹ Characteristic symptoms in infancy include periorificial (oral, anal, genital) and acral dermatitis, diarrhea, behavioral and mental changes, neurological disturbances, and secondary bacterial and fungal infections. In older children, failure to thrive, anorexia, alopecia, nail dystrophy, and repeated infections are more common. Zinc deficiency may be due to inadequate intake, malabsorption, excessive loss, or a combination of these factors. If treated early, most of the symptoms are reversible and usually leave no sequelae. The pathophysiology of AE is not fully understood.²⁻⁴ Untreated patients usually die within the first few years of life. They have severe growth retardation, dermatitis,

alopecia, secondary bacterial and fungal infections, and neurological and behavioral changes.^{5,6} No race or sex predilection has been reported. AE symptoms generally manifest when an infant is weaned from breastfeeding or earlier if the infant is formula fed.²⁻⁴ Full-term breastfed infants can develop signs of zinc deficiency late in the course of lactation because some nursing mothers have low levels of zinc in their breast milk.⁷⁻⁹ AE-like symptoms have been described in older children and adults who are on prolonged parenteral nutrition without zinc supplementation.^{6,10} Erythematous to vesiculobullous or pustular lesions leading to dry, scaly, or eczematoid rash distributed around periorificial and acral areas of the body are characteristic of AE. The borders of affected areas are sharply demarcated and have an accentuation of craquelé like scale at the periphery. Paronychia may be present. Partial or total hair loss may be evident.²⁻⁴ Zinc deficiency causes all these clinical symptoms, which are easily and rapidly reversible with zinc supplementation and therapy achieves a survival rate of 100%. In most patients with AE, plasma zinc concentrations are

Address for Correspondence

Squadron Leader Dr. Arfan-ul-Bari
Consultant Dermatologist
PAF Hospital, Sargodha.
Ph# 051-561-33799, 5583688
Email: albariul@yahoo.com

low (<50 µg/dl) but this is not diagnostic. Reference range zinc concentrations have been reported in patients with AE and low zinc concentrations may be seen in patients without AE.¹¹ Plasma level range is 70–110 µg/dl. Leukocyte zinc level is very sensitive test for early minor changes, but is more expensive. Urinary zinc levels are highly unreliable depending upon body state of zinc. Normal value is 200–500 µg/24 hrs. Hair and saliva zinc levels are rarely needed. Production of serum alkaline phosphatase depends on zinc; therefore, a low level of alkaline phosphatase may support an AE diagnosis.^{12,13} Skin biopsy reveals non-specific eczematous changes while intestinal mucosal biopsies show loss of villous architecture with increased cell infiltration in the lamina propria of patients with AE. These are not routinely done. Treatment is essentially with dietary or intravenous supplementation. Dietary supplementation with 2-3 times the recommended daily allowance, 30-55mg/day of elemental zinc dramatically reverses the manifestations within hours to days. Improvement in mental status and diarrhea is seen within 24 hrs. Severely infected and erosive lesions show reversal within 1-2 weeks. A surge of hair growth may be detected within 3-4 weeks. Zinc compounds, which appear to be effective, include zinc complexes with sulfates, acetates, gluconate, chloride, and amino acid chelate.^{2-4,14,15} For most zinc deficient individuals a single capsule of 220mg zinc sulfate contains 55 mg of elemental zinc. In AE, zinc therapy is maintained throughout the patient's life span, although periods of remission have been reported. Exacerbation during pregnancy or the stress of disease may require an increase in therapy. In acquired zinc deficiency, treatment can be stopped after the precipitating cause has resolved. Zinc-

containing foods include oysters, crab, meat products, human milk, dried beans, and lentils may also be encouraged. Oral diodoquine has also got a therapeutic role probably by enhancing the absorption of zinc.¹⁶

Case histories

Three siblings with respective ages of 11, 8 and 3 years from a low socioeconomic group family belonging to Tehsil Gujar Khan, District Rawalpindi presented in Military Hospital, Rawalpindi with history of recurrent weeping and crusting lesions around the mouth and perineum along with loose motions off and on. The children were asymptomatic till the age of about 4 months. They started developing itchy weeping and crusted lesions over skin around mouth and perineum during period of weaning. Later similar lesions appeared on hands, feet and flexures of upper and lower limb (**Figures 1**).



Figure 1 Three affected children of a family showing skin involvement in acrodermatitis enteropathica

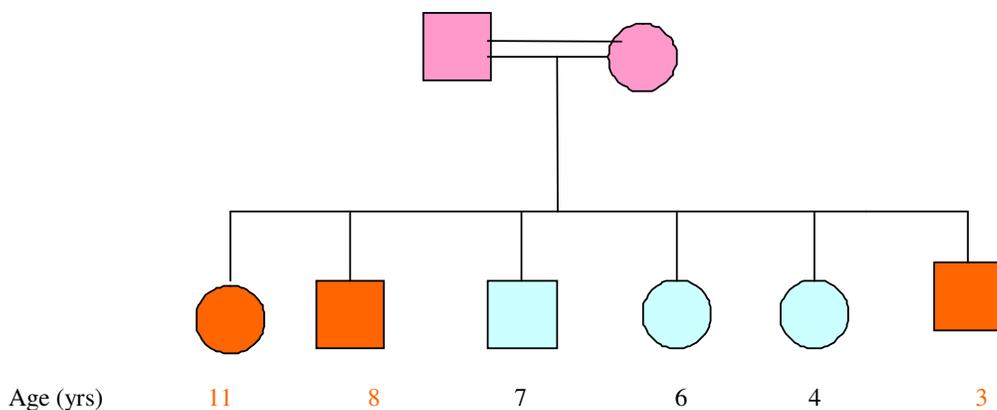


Figure 2 Pedigree showing whole family. Filled circles and squares show diseased females and males.

All the three patients used to have episodic loose motions which were watery in consistency, 50–100 ml in volume, 3–4 times a day lasting for 3–7 days. They did not have jaundice, joint pains, or abdominal distension. Their parents did not have any history of blood transfusion, extramarital sexual contact or intravenous drug abuse. The three patients were among the six siblings born to consanguineous parents (**Figure 2**). They were all breast fed till the age of 1–1½ yrs and were vaccinated to the age. All three had history of delayed milestones development. On physical examination all were found to be fully conscious and well oriented. There was no pallor, jaundice, cyanosis, clubbing or lymphadenopathy. Weights and heights of all the patients were slightly below the normal lower limit relevant to their age. Systemic examination was unremarkable. Periorificial and perineal areas revealed eczematous, lichenified, and hyperpigmented lesions. Similar lesions were also seen in flexures of upper and lower limbs. Angular cheilitis was present. Hair were relatively sparse and thin. Mucous membranes and nails were found to be normal. Blood profile, urine examination, liver function tests, serum

total proteins and albumin were within normal limit. Serum zinc levels were 36.5µg/dl, 31.4µg/dl and 42.7µg/dl, respectively. Histopathology revealed hyperkeratosis, hypergranulosis and epidermal hyperplasia along with upper dermal perivascular mononuclear infiltrate (consistent with chronic eczematous changes). A diagnosis of acrodermatitis enteropathica was made and patients were treated with zinc sulfate 2 mg/kg/day. One week after start of treatment, skin lesions improved remarkably. On follow up visit after 1 month diarrhea had settled and there was a definite improvement in the general health of the patients.

Discussion

Acrodermatitis is an inherited disorder transmitted as an autosomal recessive trait and is caused by inability to absorb sufficient zinc from diet. In fact the term acrodermatitis is now being used to include all the patients with acral dermatitis due to zinc deficiency, hereditary or acquired in origin. In order to understand the disease, a brief overview of zinc metabolism remains essential. The adult body contains 2–3 gm of zinc, which exists almost totally in its oxidized (Zn^{+2})

form and does not undergo further oxidation or reduction. Normally about 30% of daily intake is absorbed and 60–70% of it gets bound to albumin and 10–20% to α -2 microglobulins.^{12,13} Because oral or intravenous zinc supplementation in patients with AE improves their symptoms, a defect in zinc metabolism (especially in intestinal absorption or bioavailability of zinc in the intestinal lumen) is a possible pathological pathway. Grider and Mouat¹⁷ described differences in 2 novel proteins in the fibroblasts carrying the AE mutation. Wang¹⁸ has recently mapped the AE genetic locus to band 8q24.3. In infants with AE, an absence of a binding ligand may contribute to zinc malabsorption during weaning. Such a ligand has been identified in normal pancreatic secretions as well as in human milk.¹⁹ Other causes, such as high phytate concentrations found in cereals and soy milk, inhibit zinc absorption. Geophagia, also decreases zinc absorption.²⁰ Periorificial and acral dermatitis can be observed with many other conditions, including biotin deficiency, atypical epidermolysis bullosa, generalized and local candidiasis, atopic dermatitis, abnormality of essential fatty acid metabolism, seborrheic dermatitis, and kwashiorkor. If differentiation becomes difficult on clinical grounds, therapeutic trial with zinc can be distinctive in such cases. Zinc can also have a role in other diarrhea-like illnesses and more often zinc deficiency occurs in association with other micronutrients deficiencies especially iron and copper and replacement therapy in such cases has proved very beneficial.^{15,21} Reduction in infant mortality was also noted by zinc replacement therapy in case of premature infants.²⁴

Conclusion

Acrodermatitis enteropathica remains one of the most intriguing disorders known to medical science. Seldom have so many physical signs and symptoms, been attributable to deficiency of one single element. All of these signs and symptoms are dramatically reversed by single dietary supplement of zinc.

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