Journal of Pakistan Association of Dermatologists 2007; **17**: 116-121.

Case Report

Role of correct dose of zinc sulphate in the treatment of acrodermatitis enteropathica in two siblings

Asher Ahmed Mashhood

Consultant Dermatologist, Combined Military Hospital, Multan

Abstract Acrodermatitis enteropathica is a rare autosomal recessive disorder, caused by impaired absorption of zinc from gastrointestinal tract and results in several physical and psychological effects. It typically causes perioral and perigenital eczematous rash. The disease is treated by zinc sulphate powder but while calculating the dose of powder, due attention is not given to the amount of elemental zinc per mg of zinc sulphate powder, resulting in slow and incomplete response to the treatment.

Key words
Acrodermatitis enteropathica, zinc sulphate, elemental zinc.

Introduction

Acrodermatitis enteropathica (AE) is a rare inherited disorder transmitted as an autosomal recessive trait. The clinical syndrome is characterized by basic triad of acral dermatitis, alopecia and diarrhea. The distribution of scaly and vesicobullous rash on face, hands, feet and anogenital area is now considered pathognomonic of the disease. Prior to the discovery that this disorder is caused by zinc (Zn) deficiency,[1] the disease was fatal in infancy and early childhood. It is now dramatically cured by simple dietary supplementation and Zn salts. Over years of clinical experience it is found that despite of the correct diagnosis, mistakes are committed in calculating the correct dose of zinc sulphate powder. This article highlights this error in the management of patients suffering from AE.

Address for correspondence
Maj. Dr. Asher Ahmed Mashhood,
Consultant Dermatologist,
Combined Military Hospital, Multan.
Tel # 061-5316154
E-mail: asherahmed67@yahoo.com

Case report

My patients were a brother and sister, three- and four-year-old, respectively. They were brought to skin out-patient department by their parents with the complaints of diarrhea off and on, poor appetite, inability to gain weight, irritability and diffuse skin rash for the last 2 years. The boy had a diffuse thinning of scalp hair and a scaly rash over the face (**Figure 1**) with vesicobullous lesions and crusts surrounding the lips. The anogenital region had a bright red and eroded surface surrounded by a crusted border (**Figure 2**). The baby girl was looked more sickly. She had hair thinning, scaly and erythematous rash on the face and eroded and crusted lesions surrounding nose and lips. The whole trunk was covered with eroded and crusted plaques (**Figure 3**). There were vesicobullous lesions in the

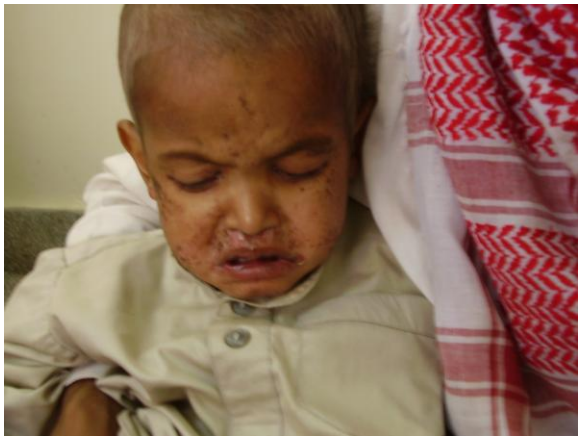

Figure 1 Diffuse thinning of scalp hairs and a scaly rash over the face.

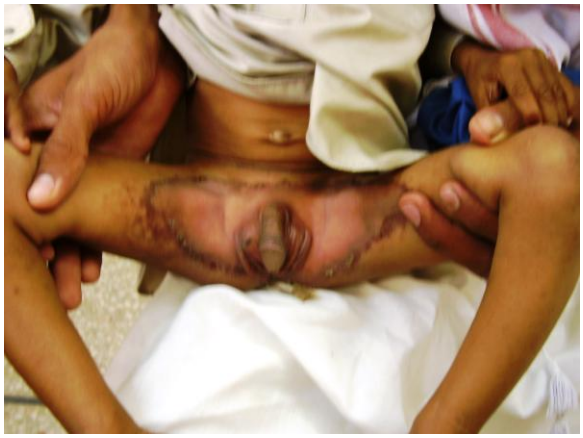

Figure 2 Bright red and eroded surface surrounded by a crusted border

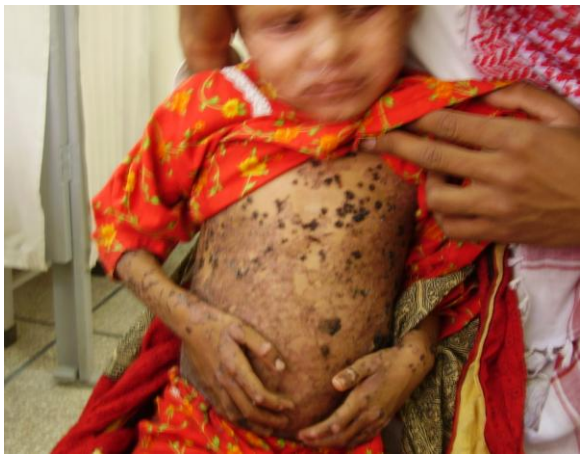

Figure 4 Eroded and crusted plaques on the trunk

palmar creases of both hands. There was severe intertrigo and perianal rash which

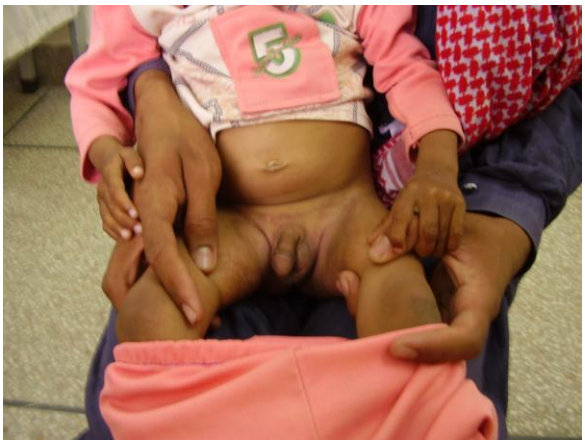

Figure 6 Appearance of the intertriginous skin of the boy after 2 weeks of treatment.

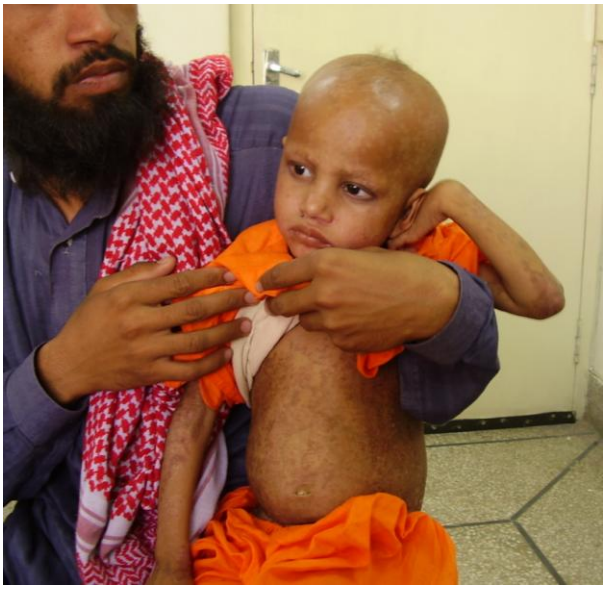

Figure 7 Appearance of the girl after 2 weeks.

was raw, oozing and had a vesicular and crusted border. The patients were taken to several dermatologists and were prescribed oral Zn powder several times with only partial relief of their signs and symptoms. They were not using any treatment for the last 2 months.

Serum Zn and albumin levels were done. They were 35 µg/dL and 25 g/L, respectively in the boy and 30µg/dL and 20 g/L, respectively in the girl. Based on the clinical appearance and laboratory tests the

diagnosis of 'acrodermatitis enteropathica' was made in both the patients and they were advised zinc sulphate powder in a dose of 2 mg/kg body weight. The weights were 20 kg and 24 kg of the boy and girl, respectively. Since 4.4 mg of Zn sulphate powder contains only 1 mg of elemental Zn the daily dose calculated was 176 mg and 210 mg daily, respectively. The measured powder was mixed in glucose powder of equal amount and dispensed in 4 sachets of equal amount, to be given four times daily.

The clinical appearance improved dramatically in both children. They became active, started taking normal meals, the diarrhoea stopped and there was marked and rapid improvement in the skin lesion (**Figure 4** and **5**). After 2 weeks the lesions almost healed completely but the patients were continued with oral Zn for another 4 weeks.

Discussion

AE is a very intriguing disorder, known to medical science because seldom in human physiology so many physical and emotional signs and symptoms are attributed to one single element, and all of which are rapidly reversed by simple Zn supplementation. Zn is an important cofactor of numerous enzymes and transcription factors, and it acts as an intracellular mediator, similarly to calcium. It is important for several functions such as gene expression, immunity, reproduction or protection against free radicals damage. Since Zn was discovered in 1940 to be present in carbonic anhydrase, the list of Zn metalloenzymes has grown to over 200.[2]

All body tissues contain Zn. Muscle, bone, and the prostate gland has the richest stores. In the skin, Zn is concentrated in the epidermis, which contains up to five or six times greater concentration than the dermis.[3] Zn also concentrates in hair, but changes in host Zn nutriture will be reflected in hair Zn concentration only after prolonged periods of deprivation (or excess), so its quantization is unreliable for assessment of short-term or recent events.

The adult body contains 2-3 g of Zn, which is about half the iron. Although the role of Zn for normal growth and development in rats was discovered in 1934, it was not established until 1974 that this trace element is also important for humans. The recommended daily allowance (RDA) was set at 15 mg/day. The normal diet provides 12-15 mg of Zn daily. Body stores replenish supplies during times of reduced intake; however, during periods of dietary deprivation, the body falls into negative Zn balance.

Zn homeostasis results from a coordinated regulation by different proteins involved in uptake excretion and intracellular storage/trafficking of Zn. These proteins are membranous transporters, belonging to the ZIP and ZnT families, and metallothioneins.[4] There are four mammalian Zn transporter ZnT-1 to ZnT-4. ZnT-1 is located in the plasma membrane of all cells,[5] ZnT-2 appears to function in cytoplasmic vesicular Zn uptake and efflux, ZnT-3 is associated with vesicular Zn uptake in neurons and in the testes and ZnT-4 is thus far found to be concentrated in the plasma membrane of cells in the mammary gland and the brain.[6] A fifth metal

transporter, called divalent cation transporter (DCT-1), is associated with the transport of several cations (Fe^{2+}, Cu^{2+}, Cd^{2+}, Mn^{2+}) in addition to Zn.[7] Citrates,[8] prostaglandin E2[9] and picolinic acid[10] are bound to Zn and enhance its absorption. Overall state of total-body Zn also influences Zn absorption. Hence Zn depleted individuals will absorb Zn much more avidly than normal. It is also found that in human milk Zn is bound to low-M*r* ligand compared to bovine milk and hence more easily absorbed. Therefore AE commonly occurs in children when they are weaned off from, breast milk.

In AE the main defect is in early stage of Zn nutriture where the chemical form and structure in which dietary Zn is presented to intestinal mucous brush borders and defect in Zn binding ligands and Zn transporters, SLC39A4.[11] Its absorption from intestinal villous brush borders into the blood and its transport to liver and kidney appears to function normally in AE. In recent years a number of infants with presumed hereditary AE have been reported who had all the typical findings of AE as outlined above, but who were found subsequently to have hypozincemia as a result of a very low concentration of Zn in their mother's milk.[12] No specific genetic reasons were found for the low maternal milk Zn levels. The mothers most likely became marginally Zn deficient due to the increased demands for Zn during pregnancy and lactation. Such reports suggest that any breast-fed infant (especially premature infants) who develops an acral dermatitis of even mild degree should be checked for Zn status, and the maternal milk should also be checked.[13]

A possible role for biotin in AE has been proposed, particularly in premature infants with Zn deficiency who responded better to a combination of Zn and biotin than to Zn alone.[14] A number of disorders and post-surgical states are now recognized to be causes for Zn deficiency. The most common are those involving the gastrointestinal tract, such as chronic inflammatory bowel disease with diarrhea and/or malabsorption, worm infestations, steatorrhea, pancreatic insufficiency, and cirrhosis or surgically-induced conditions such as total or partial gastrectomies and bowel resections, with or without blind-loop syndromes. Any catabolic chronic disease like collagen vascular diseases, malignancy and use of anti-metabolites, alcoholics,[15] high phytate content in diet and total parenteral nutrition also contribute to Zn deficiency.

The laboratory verification of Zn deficiency is the same for hereditary deficiency (AE) or any of the acquired forms. Plasma or serum Zn levels are currently the easiest, best, and most commonly used method for assessing Zn status. Normal plasma levels are 70-110 µg/dL. Urinary Zn excretion is highly variable under normal circumstances but gradually decreases as Zn deficiency progresses. The normal urinary excretion ranges from 200 to 500 µg per 24 h. Hair Zn concentration is commonly measured; however, reflects only the long-term Zn status. Its use and interpretation will therefore depend upon the clinical situation and type of information desired. Serum alkaline phosphatase activity is a moderately sensitive indicator of Zn status, although not a particularly early marker of deficiency. Its activity remains near normal until profound and prolonged deficiency exists. It should

also be emphasized that specimen collections and laboratory technique are important. It is, therefore, recommended to use Zn-free vacuum tubes and stainless steel needles, avoid contact with rubber stoppers (they contain Zn), avoid hemolysis, separate plasma or serum from cells within 45 min, and use anticoagulants that are low in Zn or Zn-free. There is also a diurnal rhythm in plasma Zn concentration; morning fasting specimens are recommended for the most accurate results. The treatment of Zn deficiency is essentially that of dietary or intravenous supplementation with Zn salts, no matter what the etiology. In most instances, dietary supplementation with two to three times the RDA in doses of 30 to 55 mg of elemental Zn^{++} daily will be adequate to restore a normal Zn status within days to a few weeks, depending on the degree of depletion. In all circumstances, a rapid clinical response will occur with dramatic reversal of many manifestations within hours to days. Severe infected and erosive skin lesions will heal within 1 to 2 weeks without additional topical therapy. Diarrhea, if present, often stops within 24 h. Rapid improvement in mental disturbances is usually detectable within 24 to 48 h. In children, a surge of total-body and hair growth can be detected within 3 to 4 weeks after commencing Zn therapy.

Any of the Zn compounds available appear to work well (Zn sulfate, Zn acetate, Zn gluconate, Zn chloride, amino acid chelates). However, $ZnSO_4$ has been recommended more for oral supplementation, and $ZnCl_2$ for intravenous use. Dosage prescribed must be based on the amount of elemental Zn present in the preparation, which varies from one compound to another. For example, 4.4 mg of $ZnSO_4 \cdot 7H_2O$ contains approximately 1 mg of elemental Zn. The dose is 2 mg/kg/day for oral and 0.2-0.3 mg/kg/day for parenteral treatment. Lately, Atco Laboratories have launched a dry suspension by the name of "Zincat®" containing 10mg of elemental zinc per 5 ml. The use of this suspension will simplify the calculations of Zn needs to be given to a patient. A reciprocal interaction with copper is well recognized.[16] Patients receiving prolonged oral Zn supplementation are prone to develop hypocupremia as a consequence of long-standing hyperzincemia. One adverse effect of hypocupremia is a refractory microcytic anemia that will not respond to iron therapy until the serum copper level is normalized.[17] Neutropenia, immune dysfunction, and hypoceruloplasminemia also occur with hypocupremia.[18]

It is, therefore, recommended that patients on long-term Zn therapy should be monitored periodically with the following tests: plasma Zn concentrations taken as a fasting AM specimen to regulate dosage, complete hemogram with erythrocyte indices, leukocyte differential count, serum copper level, and a stool examination for occult blood.

References

1. Moynahan EJ, Barnes PM. Zinc deficiency and a synthetic diet for lactose intolerance. *Lancet* 1973; **1**: 676-7.
2. Vallee BL, Galdes A. The metallobiochemistry of zinc enzymes. *Adv Enzymol* 1984; **56**: 284-430.
3. Molokhia M, Portnoy B. Neutron activation and analysis of trace elements in skin: III. Zinc in normal skin. *Br J Dermatol* 1969; **81**: 759-62.

4. Chimienti F, Aouffen M, Favier A. Zinc homeostasis-regulating proteins: new drug targets for triggering cell fate. *Curr Drug Targets* 2003; **4**: 323-38.
5. McMahon RJ, Cousins RJ. Regulation of the zinc transporter ZnT-1 by dietary zinc. *Proc Natl Acad Sci* 1998; **95**: 4841-6.
6. Huang L, Gitscher J. A novel gene involved in zinc transport is deficient in the lethal milk mouse. *Nat Genet* 1997; **17**: 292-7.
7. Gunshin H, Mackenzie B, Berger UV *et al*. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 1997; **388**: 482-8.
8. Menard MP, Cousins RJ. Effect of citrate, glutathione and picolinate on zinc transport by brush border membrane vesicles from rat intestine. *J Nutr* 1983; **113**: 1653-6.
9. Song MK, Adham NF. Evidence for an important role of prostaglandin E-2 and F-2 in the regulation of zinc transport in the rat. *J Nutr* 1979; **109**: 2152-9.
10. Evans GW, Johnson PE. Characterization and quantitation of a zinc binding ligand from human milk. *Pediatr Res* 1980; **14**: 870-80.
11. Meftah SP, Kuivaniemi H, Tromp G. A new mutation in exon 3 of the SCL39A4 gene in a Tunisian family with severe acrodermatitis enteropathica. *Nutrition* 2006; **22**: 1067-70.
12. Lee MG, Hong KT, Kim JJ. Transient symptomatic zinc deficiency in a full-term breast-fed infant. *J Am Acad Dermatol* 1990; **23**: 375-9.
13. Kharfi M, Zaraa I, Kury S. Acrodermatitis enteropathica in full-term breast fed infant. *Ann Dermatol Venereol* 2005; **132**: 246-8.
14. Lagier P, Bimar P, Seriat-Gautier S *et al*. Zinc and biotin deficiency during prolonged parenteral nutrition in the infant. *Presse Med* 1987; **31**: 1795-7.
15. Taniguchi S, Kaneto K, Hamada T. Acquired zinc deficiency associated with alcoholic liver cirrhosis. *Int J Dermatol* 1995; **34**: 651-2.
16. Kirchgessner M, Schwarz, FJ, Schnegg A. Interactions of essential metals in human psychology. In: Prasad AS, ed. *Clinical, Biochemical, and Nutritional Aspects of Trace Elements.* New York: Alan R Liss; 1982. p. 477-512.
17. Solomons NW, Pineda O, Viteri F, Sandstead HH. Studies on the bioavailability of zinc in humans: mechanism of the intestinal interaction of non-heme iron and zinc. *J Nutr* 1983; **3**: 337-49.
18. Sandstrom B, Cederblad A, Lindblad BS, Lönnerdal B. Acrodermatitis enteropathica, zinc metabolism, copper status and immune function. *Arch Pedatr Adolesc Med* 1994; **148**: 980-5.