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Acrodermatitis enteropathica: the need for sustained high dose zinc supplementation

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Abstract

Acrodermatitis enteropathica (AE) is a rare congenital disorder owing to an abnormality with intestinal absorption and/or transportation of zinc. We describe two male siblings, who presented with evidence of both acute and chronic zinc deficiency, despite being diagnosed with AE very early in life. We wish to highlight the importance of sustained high-dose zinc supplementation and regular monitoring in AE cases. Proper counselling of parents about the need for life long supplementation and increasing requirements with age is essential.

Keywords: zinc deficiency, acrodermatitis enteropathica

Introduction

Acrodermatitis enteropathica (AE) is a rare congenital disorder with autosomal recessive inheritance owing to an abnormality with intestinal absorption and/or transportation of zinc. Moderate to severe (acute) zinc deficiency usually presents with eczematous to vesiculobullous, pustular and erosive lesions. Psoriasiform lesions are seen in mild or chronic zinc deficiency [1, 2]. We report two male siblings with AE who presented with evidence of acute and chronic zinc deficiency simultaneously, despite being diagnosed very early in life.

Case Synopsis

Two male siblings, 17 and 13 years old, born of a 2nd degree consanguineous marriage presented with complaints of asymptomatic red rashes and fluid filled lesions on-and-off since 6 months of age. They were diagnosed to have AE and advised to continue life-long zinc supplementation. Since then, they have been on zinc-containing vitamin supplements on-and-off with exacerbations on stopping the medication. The elder sibling came with a history of non-healing ulcers and pus-filled lesions over the legs over the past 6 months, which had not improved in spite of taking zinc. Developmental milestones were normal. He was a vegetarian by diet and gave a history of weight loss of approximately 5kg in the last one month. The younger sibling had similar complaints but limited to the legs. There was no history of diarrhea, photosensitivity, or trauma induced blistering in both the siblings. There were no eye or psychiatric complaints.

On examination, the elder child was pale, with normal height, but his weight for age was below the 50th percentile. Cutaneous examination revealed multiple erythematous patches with areas of atrophy and depigmentation, symmetrically over the dorsum of both hands, fingers, toes, and dorsum of feet extending onto the lower part of legs; some areas showed crusting (**Figure 1A, B**). A large non-healing ulcer measuring 6×12cm, covered with hemorrhagic crusts was present over the medial aspect of the left

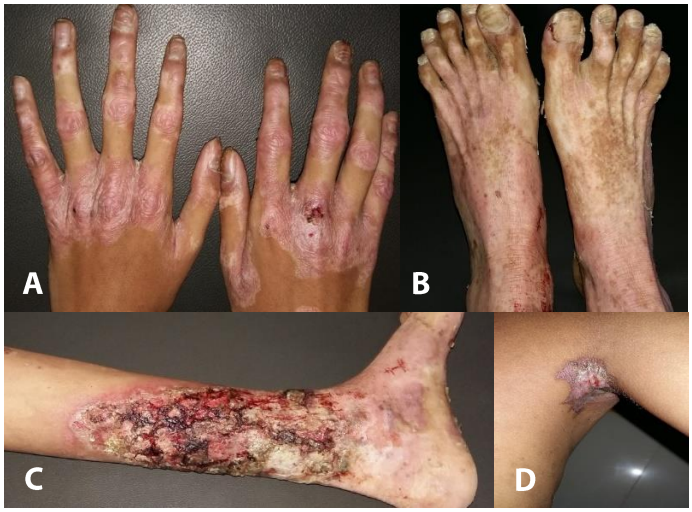

Figure 1. ***A, B****) Dorsum of hands and feet showing atrophic depigmented patches with Beau's lines over the finger and toe nails in the elder sibling.* ***C****) Ulcer over the medial aspect of left leg with overlying hemorrhagic crust and surrounding erythema.* ***D****) Hyperpigmented scaly plaque in the left axilla.*

leg (**Figure 1C**). A similar ulcer of 4×3cm was present adjacent to the right knee. Hyperkeratotic scaly psoriasiform plaques were present over both elbows, antecubital and popliteal fossae, and axillae (**Figure 1D**). There were erythematous scaly patches in the perioral and perinasal areas, ear lobules, and nape of neck, suggestive of seborrheic dermatitis. Erythema and exfoliation was present over palmar and plantar creases and scrotum. His scalp and body hair was diffusely sparse. He had an absence of axillary and beard hair and sparse pubic hair, which suggested incomplete development of secondary sexual characters. Graying of hair over his scalp was seen and the hair pull test was positive. On microscopic examination of the hair, the cortex was thinned out and transverse striations were present (**Figure 2A**). There was loss of transparency of all the finger and toe nails with multiple Beau lines (**Figure 1A, B**). The younger sibling had scaly patches with areas of hyper and hypopigmentation over dorsum of feet, fingers, and toes (**Figure 2B**). He also had a few bullae over the palmar creases, sparseness of hair on the scalp, and Beau lines of the nails (**Figure 2B**).

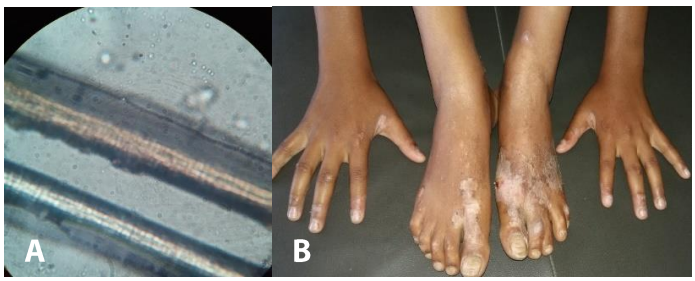

Figure 2. ***A****) Scalp hair microscopy depicting transverse striations.* ***B****) Scaly patches over the dorsum of feet and toe web-spaces in the younger sibling.*

Routine investigations were normal. Serum zinc levels in the elder and younger sibling were 38.48 µg/dl and 36.91 µg/dl, respectively (Normal: 66.0-110.0 µg/dl). Skin biopsy from the scaly plaque on right elbow showed epidermis with scale crust, irregular acanthosis, and broad rete ridges with edema in the papillary dermis along with congested blood vessels. On higher magnification, a single layer of pale cells was seen. Serum alkaline phosphatase enzyme and serum testosterone levels were mildly reduced. With all the above findings, a diagnosis of acrodermatitis enteropathica with exacerbation was made in both the siblings. Within one week of starting elemental zinc in the form of zinc sulfate orally at a dose of 50mg twice daily (dose of 3 mg/kg), skin lesions of the elder sibling showed dramatic improvement. The younger child was supplemented with elemental zinc orally50 mg once daily. Regular follow-up is being done every 3 months with clinical examination and serum zinc level estimation. Both siblings are maintained at 3 mg/kg/day supplementation of zinc and are in remission.

Case Discussion

Approximately 10% to 30% of dietary zinc is absorbed in the small intestine using a transcellular zinc-specific transporter, Zip4, coded by the *SLC39A4* gene located on the long arm of chromosome 8. Several mutations in this gene have been identified in AE [1]. The characteristic clinical triad of AE includes periorificial and acral dermatitis, diarrhea, and alopecia. However, the triad is seen in only 20% of cases [3]. In a Tunisian study of 29 cases of acrodermatitis enteropathica, they found cutaneous involvement in all cases, whereas the clinical triad was seen in only 27.58% of patients [4].

Children with AE commonly present at 1-2 weeks after weaning with acral and periorificial (around mouth, eyes, genitalia) symmetrical, eczematous

plaques that become vesicular, bullous, pustular, or erosive with characteristic crusting at the edges. The perioral eruption usually spares the upper lip giving it a 'U-shaped' or 'horseshoe-shaped' appearance [1, 5]. Infants are described as listless and apathetic. Zinc deficiency can lead to failure to thrive and can be fatal if untreated. Immune abnormalities place AE patients at an increased risk for superinfection by bacteria, commonly *Staphylococcus aureus* and yeast such as *Candida albicans*. These infections do not respond to topical therapy unless zinc deficiency is corrected [1, 6]. Zinc-responsive areas resembling vitiligo hypopigmentation have also been reported [7]. The elder sibling exhibited infected non-healing ulcers on legs and vitiliginous lesions over hands and feet.

Structural changes of the hair that may be observed in AE are broken spearhead-like endings, transverse striation of the shaft, pseudomonilethrix, longitudinal splits, and bayonet hairs. Severe zinc deficiency causes total arrest of nail growth. Transverse depressions (Beau lines) on the fingernails become visible about 4 weeks after zinc therapy is started and normal nail growth is re-established [8, 9]. Our patients had alopecia, transverse striations of the hair, and Beau lines on the nails. Other findings seen in AE are delayed wound healing, alopecia, paronychia, onychodystrophy, blepharitis, conjunctivitis, photophobia, stomatitis, angular cheilitis, emotional lability, and irritability [1, 4, 6]. Although hair and nail changes were present in our cases, emotional problems and eye involvement were conspicuously absent. Intermittent supplementation of zinc might explain the absence of eye and psychiatric findings.

Weissmann et al. described the occurrence of flat bullous lesions with brownish erythema in patients with acute deficiency of zinc. Oozing lesions, some with necrotic and burnt-skin like appearance have been observed in bedridden patients [10]. Our cases had bullous lesions over the palmar creases and the elder sibling had ulcers with a necrotic base, which are suggestive of acute zinc deficiency. Brownish scaly or psoriasiform lesions on pressure points, like knees and elbows, and a seborrheic dermatitis-like picture, as in our elder sibling, have been described in subacute or chronic zinc deficiency. Children and adolescents with chronic deficiency may also present with growth retardation, hypogonadism (in males), dysgeusia, and abnormal dark adaptation [2, 8]. The elder sibling had absent secondary sexual characters with reduced serum testosterone levels.

The diagnosis of AE is based on clinical and laboratory abnormalities. Low zinc levels (<70 µg/dl fasting or <65 µg/dl non-fasting) are indicative of AE [1, 5], No correlation between serum zinc and specific clinical features was observed in one study [4]. Consistent with this observation, our elder sibling, who had severe involvement had higher zinc levels than the younger one with minimal involvement. Zinc-dependent enzymes such as alkaline phosphatase may be decreased as in our case. Molecular genetic analysis of *SLC39A4* is confirmatory. Zinc supplementation has a rapid and dramatic effect that reverses all the changes. Skin lesions improve first following supplementation within 24-48 hours of zinc supplementation [1, 4].

Irregular intake of zinc supplements and inadequate dosage can lead to exacerbations with features of chronic deficiency, the clinical presentation of which may not be classical as in our cases. Regular monitoring of children with serum zinc measurements every 3 to 6 months is a must to identify signs of inadequate dosage. Copper and iron levels should also be assessed regularly as a result of their interaction with zinc [1]. Excessive zinc supplementation can lead to increased expression of metallothionein in enterocytes, which preferentially binds copper. As a result, most of the copper ingested is not absorbed but rather sloughed off with the enterocytes into the lumen leading to hypocupremia [11].

There is no clear consensus or recommendation on the exact dose of zinc to be given in AE, although it is agreed by most that patients need life-long supplementation of 3 mg/kg elemental zinc [1-3, 12]. Some advocate regular 1-2 mg/kg/day of elemental zinc supplementation in AE [13] with higher dose (5-10 mg/kg) when there is an exacerbation [4]. Zinc sulfate or zinc gluconate can be used. The commercially available 220mg zinc sulfate tablets contain 50mg of elemental zinc. In a Tunisian study

on 29 cases of AE they found relapses in many cases during adolescence, and also within 15 days of interruption of treatment (cutaneous signs were the first to recur), [4]. A recent article has also highlighted the importance of sustained high dose zinc supplementation in AE cases [14]. Whether AE patients need higher doses during infection, stress, or adolescence needs to be studied further.

Conclusion

With this report, we would like to highlight the importance of sustained high dose zinc supplementation and regular monitoring of AE patients for signs of deficiency. Proper counselling of parents about the need for life long supplementation and increasing requirements with age is essential.

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