

Transient Symptomatic Zinc Deficiency in a Breastfed Infant Associated with Low Zinc Levels in Maternal Serum and Breast Milk Improving after Zinc Supplementation: An Uncommon Phenotype?

Abstract

Acrodermatitis enteropathica (AE) is a rare, autosomal-recessive disorder of neonatal zinc deficiency due to *SLC39A4* (intestinal zinc transporter, Zip4) gene mutation with onset after weaning while breastfeeding during this period will be protective. Transient symptomatic zinc deficiency is also acquired rarely in breastfed infants with increased zinc requirements and/or inadequate concentration of zinc in breast milk. The nursing mothers of transient symptomatic zinc deficiency infants show *SLC30A2* (mammary epithelial zinc transporter, ZnT-2) gene mutation and abnormally low zinc levels in the breast milk despite normal serum zinc levels, which do not improve after zinc supplementation. A 2-month-old breastfed male infant had AE-like clinical features of zinc deficiency for two weeks. His symptoms and low serum zinc levels improved rapidly after zinc supplementation. The mother also had low serum and breast milk zinc concentration and both improved after oral zinc therapy indicating a non-heritable phenotype. The relevant literature is reviewed and significance of dietary zinc supplementation during pregnancy/lactation is emphasized.

Keywords: *Acrodermatitis enteropathica, breastfed-infant, dietary zinc, hypozincemia, lactation, zinc*

Introduction

Zinc deficiency in infancy in its classic form is known as acrodermatitis enteropathica (AE). It is a rare autosomal-recessive disorder of impaired intestinal zinc absorption due to mutations in *SLC39A4* gene mapped to 8q24.3 chromosome encoding Zip4 zinc transporter essential for intestinal absorption of zinc.^[1-3] It manifests clinically after weaning and is characterized by polymorphic lesions (eczematous, oozy, vesicular, bullous, pustular, burnt skin-like, psoriasiform) and/or erosive plaques with characteristic crusted edges involving skin around body orifices and over extremities accompanying with paronychia, angular cheilitis, dry and brittle hair and alopecia, diarrhea, delayed wound healing, and increased susceptibility to infections particularly for *Staphylococcus aureus* and *Candida albicans*.^[4,5] Photophobia, anemia, anorexia, hypogeusia, nail dystrophy, failure to thrive, delayed growth and puberty, and male hypogonadism ensue or it may end fatally in untreated cases. On

the other hand, more frequent is transient symptomatic zinc deficiency in first few months occurring in premature or low birth weight infants because of inadequate neonatal stores, high requirement, or sometimes from prolonged parenteral alimentation.^[5] Other uncommon cause of transient symptomatic zinc deficiency in breastfed infants has been described secondary to abnormally low zinc levels in the breast milk despite normal serum zinc levels in nursing mother.^[6,7] Zinc deficiency whether inherited or acquired has identical clinical features, which are mainly due to low zinc levels and clinical improvement is rapid, within days to weeks, after zinc replacement therapy. While AE needs lifelong treatment, treatment duration in transient neonatal zinc deficiency without relapses depends upon breastfeeding at weaning.^[8] The described case is of a breastfed infant with transient symptomatic zinc deficiency having AE-like clinical features and low serum zinc levels responding rapidly to zinc supplementation. The mother had low serum and breast milk

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How to cite this article: Vashist S, Rana A, Mahajan VK. Transient symptomatic zinc deficiency in a breastfed infant associated with low zinc levels in maternal serum and breast milk improving after zinc supplementation: An uncommon phenotype? Indian Dermatol Online J 2020;4:623-6.

Received: 07-Aug-2019. **Revised:** 17-Sep-2019.
Accepted: 08-Nov-2019. **Published:** 24-Jan-2020.

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Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_386_19

Quick Response Code:



zinc levels which improved after zinc supplementation. The relevant literature is also reviewed.

Case Report

A 2-month-old male infant was hospitalized with progressive, multiple erythematous, crusted, and glazed dermatitic lesions predominantly involving buttocks, perianal area, scrotum and prepuce [Figure 1a], cheeks, chin, pinnae, neck fold, and nostrils [Figure 1b] symmetrically for 15 days suggestive of acrodermatitis enteropathica. Few similar lesions were also distributed widely over trunk and extremities, fingers [Figure 1c], ankles, and popliteal fossae. Historically, initial lesions had developed over perianal skin and involved other sites within a week. He had poor sleep, 4-5 loose stools per day, and aversion for feeds for past 1 week. He was first child born normally to otherwise healthy non-consanguineous parents after an uneventful gestation and full-term pregnancy. No similar problem was reported in any other family offsprings. He was exclusively breastfed, weighed 4.5 kg, immunized for his age, and had normal mental and developmental milestones. He was afebrile, irritable, had minimal pallor, oral thrush, photophobia, and paronychia. He had no lymphadenopathy, hair or nail abnormality. Systemic examination and baseline laboratory investigations showed no significant abnormality [Table 1]. KOH mount and aerobic culture from skin

lesions showed no fungus or bacterial growth. His serum zinc levels were 0.8µg/dl (normal 70–115 µg/dl) estimated colorimetrically (ERBACHEM-7 Spectrophotometer)



Figure 1: (a) Extensive, sharply-defined, symmetrical, erythema with erosions with glazed surface and secondary yellowish-brownish crusts in diaper region. Burnt skin-like appearance with black crusting at the margins is characteristic. Note scrotal involvement and lesions over back. Similar lesions were over extremities. (b): Multiple erythematous vesiculopustules and crusted plaques of variable size over both cheeks, around the mouth and nostrils, and neck fold. Note characteristic expression of irritability. (c): Lesions over digits and paronychia

Table 1: Laboratory data of index patient

Laboratory investigation	Day-1	Day-7	Reference values for his age
Hemoglobin	9.6 g/dl	10 g/dl	9.0-11.5g/dl
Total leukocyte count	13200/mm ³	12800/mm ³	4000-12000/mm ³
Differential leukocyte count	N18%, L72%, M10%, E0%, B0%	N31%, L60%, M7%, E2%, B0%	N 40-60%, L 30-40%, M 2-8%, E 1-4%, B 0.5-1%
Platelet counts	444,000/mm ³	450,000/mm ³	150,000-400,000/mm ³
PCV	28%	29.6%	33-43%
Blood sugar	60mg/dl	70mg/dl	50-90mg/dl
Total serum proteins/Albumin	6.3 g/dl/3.2 g/dl	-	Total 5.1-7.3g/dl Albumin 2.2-4.8 g/dl (up to 1 year of age)
Alkaline Phosphatase	482 U/L	380U/L	150-420 U/L
Serum Zinc	0.8 µg/dl	110 µg/dl	70-115 µg/dl*
Serum Calcium	14.4 mg/dl	-	8.8-12.8 mg/dl
Serum Magnesium	2.2 mg/dl	-	1.6-2.4 mg/dl
25-hydroxy vitamin D3	4.3ng/ml	-	Deficiency <12 ng/ml Insufficiency 12-20 ng/mL Sufficient ≥20 ng/mL
Serum B12	12-267pg/ml	-	180-500 pg/ml
Serum Ferritin	233.6/ml	-	50 to 200 ng/ml at 2-5 months
C-reactive protein	Positive	-	<10 mg/L
Blood culture	Sterile	-	-
Urinalysis	Normal	-	-
X-ray chest	Normal	-	-
PA view	-	-	-
USG Abdomen	Normal	-	-
CSF analysis	Normal	-	-

N, Neutrophils; L, Lymphocytes; E, Eosinophils; M, Monocytes; B, Basophils; CSF, Cerebrospinal fluid; DLC, Differential leukocyte count; PCV, plasma cell volume; USG, ultrasonography. *Reference range for zinc is as per test kit package insert

by nitro-PAPS (2-(5-nitro-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino) phenol) method using *in vitro* kits from AGAPPE Diagnostics Ltd., India. The zinc levels in mother's serum were 12 µg/dl (normal 70–115 µg/dl) and 14 µg/dl in the breast milk (normal 16.0–536.0 µg/dl, median 166.0 µg/dl at two months of postpartum).^[9] Her complete blood counts and serum biochemistry including serum calcium (9.2 mg/dl), magnesium (2.1 mg/dl), albumin (3.9 gdl), and alkaline phosphatase (88 U/l) levels were within the reference range.

Treatment with oral zinc 1 mg/kg/day of elemental zinc (zinc gluconate oral solution containing elemental zinc ≡ 4 mg/ml) in two divided doses was initiated overnight along with bland emollients topically. Mother was also given elemental zinc (1 mg/kg/day) orally as zinc sulfate 220 mg ≡ 50 mg elemental zinc, and advised to continue breastfeeding. Clinical symptoms of irritability, photophobia, diarrhea, sleep, and acceptance for feed improved rapidly by next morning after first dose itself. The serum zinc levels improved to 8.2 µg/dl after 2 doses of oral zinc. His skin lesions resolved completely [Figure 2a-c] and serum zinc levels were 110 µg/dl after 1 week at discharge from hospital. The serum and milk zinc levels in mother also improved to 166 µg/dl and 160 µg/dl, respectively, after 1 week of zinc supplementation. The baby was completely normal on follow-up visit after 2 months. Both had discontinued zinc supplementation a month after leaving the hospital. However, zinc levels in serum or breast milk could not be re-estimated. The mother was advised to wean the baby at 6 month onwards. They did not follow-up further.

Discussion

Zinc is an essential micronutrient for humans that form vital component of over 2000 transcription factors and

more than 300 metallo-enzymes (carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase, RNA polymerases).^[10] Its significance as a micronutrient vital for growth, development, and immune function and its supplementation in low birth weight infants and children is well recognized now.^[11] Although neonatal hepatic stores of zinc from intrauterine life are sufficient to meet the demand during 4–6 months of postnatal life, this may not happen for premature or small-for-gestation infants because of their poor neonatal zinc stores.^[12] The zinc nutrition, mostly from breast milk, in first 3 months postnatally is adequate. However breast milk zinc concentration, which is highest during early period of lactation, declines sharply during the first 3 months and steadily through 7 months and thereafter coinciding with weaning but the infant's requirement increases leading to deficiency states unless zinc is supplemented in daily dietary intake.^[9,13]

Acquired transient zinc deficiency in breastfed infant due to low zinc concentration in breast milk of nursing mothers that does not improve despite zinc supplementation is attributed to a mutation in the *SLC30A2* gene mapped to chromosome 1p36.11 encoding ZnT-2 zinc transporter in humans.^[7,14,15] It is associated with low mammary epithelial zinc transport in mother and is different from lethal milk mice due to murine *SLC30A4* gene mutation (ZnT-4).^[15,16] Recently, Lee *et al.*^[17] demonstrated that genetic variants in *SLC30A2* (ZnT-2) mutation have profound consequences on zinc pools. This affects key cellular functions in mammary epithelial cells that may lead to breast dysfunction and decreased secretion of zinc into breast milk which otherwise contains adequate zinc for infantile requirements up to 6 months. Reported cases suggest that this defect is perhaps inherited as an autosomal recessive or X-linked disorder.^[14] However, the genetic defect in mother mostly remains unrecognized although she represents a classic genotype and low milk zinc phenotype while the symptomatic presentation is exclusive to the breastfed infant as was also observed in our case having classic transient zinc deficiency and mother showing no signs of zinc deficiency despite very low serum zinc concentration. Although we could not perform genetic studies, the absence of consanguinity and similar problem in other family offsprings, improvement of low maternal serum and breast milk zinc concentrations after zinc supplementation, and rapid therapeutic response without recurrence in our case despite discontinuing zinc supplement short while after clinical improvement are distinct and indicative of a sporadic non-inherited phenotype. Wherein, the maternal intake of low zinc-diet during pregnancy and post partum period with consequent low serum and milk zinc concentration in her remains distinctly possible in view of prevailing social taboos and customs of dietary restrictions during pregnancy and lactation when zinc requirement increases almost two folds.^[10] However, mother showing no clinical signs despite very low serum zinc concentrations and how low maternal



Figure 2: (a) Completely resolved lesions at 1 week after zinc supplementation. The child has become playful. (b): Mild residual erythema on the cheeks and (c) diaper area

intake will influence milk zinc concentrations remains less understood as studies reviewed to understand regulation of zinc metabolism and effect of nutrition and non-dietary or other host factors on this complex process have remained inconclusive. Studies involving well-nourished populations show no direct correlation between milk zinc concentration and maternal dietary zinc intake, whereas data from low zinc consuming populations have shown low mean milk zinc concentrations.^[13,18] It has been suggested that in mild-to-moderate maternal zinc deficiency, reduced milk zinc output is perhaps a maternal adjustment to chronic intake of diet low in zinc.^[13] And we tend to agree.

Although long-term follow-up is imperative in such cases to draw any conclusion, the need of maternal zinc supplementation during pregnancy/lactation and role it has in infant's optimum growth and development are emphasized.

Declaration

All authors declare that they have no competing interest and therefore nothing to declare, and have contributed significantly and take full responsibility for the manuscript. The authors of the paper are obliged to confirm that it has not been previously published.

Contributors' statement

SV obtained, compiled, and analyzed all data and prepared initial draft. AR helped in data obtaining, compiling, and literature search. VKM analyzed and interpreted data, edited, and critically evaluated the manuscript for important intellectual content. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Statement of ethics

Informed consent was obtained from parents for publication of material with the understanding that name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975 as revised in 2013.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient/parents have given their consent for images and other clinical information to be reported in the journal. The patient/parents understand that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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