Transient symptomatic zinc deficiency in an exclusively breastfed infant

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Accepted 20 May 2021

To cite: Crisóstomo M, Santos MC, Tavares E, *et al*. *BMJ Case Rep* 2021;**14**:e241754. doi:10.1136/bcr-2021-241754

SUMMARY

A 3-month-old, full term female infant, adequate for gestational age, and exclusively breastfed, was admitted with a 10 day history of generalised scaling erythematous dermatitis, affecting the face (perinasal, nasolabial folds and periauricular), acral and intertriginous areas, with irritability and failure to thrive. Her mother had been treated with isoniazid since the third trimester because of family contact with tuberculosis. Based on a diagnosis of suspected impetiginised eczema, the infant was treated with flucloxacillin and prednisolone, and maternal isoniazid was suspended, with no improvement. Investigations found low serum zinc levels in the infant (33 µg/dL; normal range (NR) >60 µg/dL), normal plasma zinc levels in the mother (111.3 µg/dL; NR 68–120 µg/dL) and lower than the normal range of zinc levels in breast milk (270µg/L; NR 1000–2500 µg/L), suggesting acrodermatitis caused by zinc deficiency. Oral zinc supplementation (3 mg/kg/day) was started with a marked improvement in skin lesions, as well as good weight gain. At the age of 6 months, after food diversification, supplementation was suspended, without any recurrence of symptoms.

BACKGROUND

Zinc deficiency in infancy has two main causes. The classic form, acrodermatitis enteropathica, is a rare autosomal recessive disorder affecting the Zip family of proteins required for normal zinc absorption in the gut.[1] The mutated gene is believed to be SLC39A4 on chromosome 8.[2] Acquired zinc deficiency, with a similar clinical presentation, so called acrodermatitis enteropathic-like, results from lower ingestion or increased demand, as happens in preterm and low birth weight infants. Insufficient intake is usually described in those exclusively breastfed, being a self-limiting and benign condition, caused by defective mammary zinc secretion, known as transient symptomatic zinc deficiency (TSZD).[3 4]

Zinc deficiency is rare but some studies have reported that the acquired deficit (including subclinical deficiencies and asymptomatic individuals) can affects up to 17% of the population worldwide, particularly in developing countries.[1] This prevalence should be interpreted with caution. Most plasma zinc is bound to albumin and is typically decreased in patients with hypoalbuminaemia, which is a frequent condition in countries with a high prevalence of poor nutrition. However, it is not clinically helpful to correct measured zinc levels to hypoalbuminaemia, because patients with low plasma zinc levels are treated empirically with zinc supplements regardless of albumin levels. The real incidence of this condition is not known.[5]

Dermatitis is frequent in paediatric patients and can be a sign of a whole spectrum of diseases, from the most frequent (eg, atopic or seborrhoeic dermatitis) to the rare conditions. It is difficult to establish a diagnosis based only on clinical presentation. A high level of suspicion is needed in infants with persistent skin disease, as an early diagnosis is essential to optimise growth and development.

This report describes a case of an exclusively breastfed infant with TSZD, manifested mainly by skin lesions. The case is relevant because of its rarity and diagnostic challenges.

CASE PRESENTATION

A 3-month-old Caucasian girl, born to non-consanguineous parents, at full term, weighing 2720 g (clinical growth charts (CDC) P10), and exclusively breastfed, was admitted with a 2 month history of dermatitis and failure to thrive. The mother's diet was balanced, with animal protein intake and low content of phytates. From the first month of life, the mother described a cutaneous symmetrical micro-vesicular rash in the malar and perineal areas, with intermittent exacerbations. Four days before admission, generalisation of a scaling erythematous rash occurred (figure 1). At this time, irritability was reported, with poor weight gain in the last 15 days. There was no history of refusal to feed, vomiting, diarrhoea, alopecia or fever.

Due to close contact with pulmonary tuberculosis, the mother had been treated with isoniazid from the third trimester of pregnancy and completed the treatment at the beginning of the hospital stay. On admission, the infant weighed 4270 g (CDC P3) and had extensive scaling erythematous dermatitis, with symmetrical lesions, including the face (perinasal, folds, nasogenians and periauricular), antecubital fossae, acral and intertriginous areas (figure 1). Perianal lesions were not present at admission, but they were noticed during the first days of hospitalisation. Marked irritability was noted (interpreted as itching), but no other signs were observed.

Generalised infected eczema was assumed and treatment with flucloxacillin and prednisolone was started. After 5 days of treatment, the skin lesions showed no improvement and she had poor weight progression.

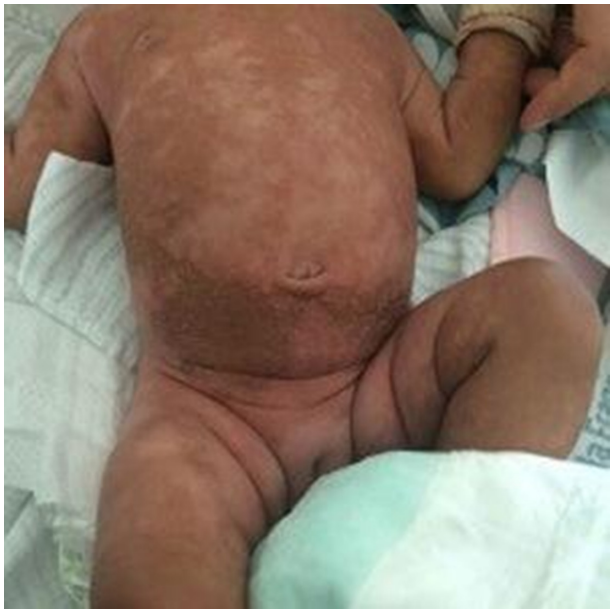

Figure 1 Transient symptomatic zinc deficiency. Erythematous crusted generalised plaques.

INVESTIGATIONS

Routine laboratory studies revealed: haemoglobin 10.9 g/dL, haematocrit 30.8%, leucocytes 14.6×10^3/uL, platelets 580×10^3/µL, reactive C protein <0.50 mg/dL, alkaline phosphatase 251 UI/L (reference range (RR) 125–449 UI/L), creatinine 0.3 mg/dL (RR 02–05 mg/dL); nitrogen urea 12 mg/dL (RR 12,8–36,4 mg/dL), aminotransferase aspartate 39 IU/L (RR 16-60UI/L), aminotransferase alanine 32 UI/L (RR 26-51 UI/L), sodium 138 mmol/L (RR 132–140 mmol/L), potassium 4.5 mmol/L (RR 3.5–5.8 mmol/L), mycobacteria tuberculosis research (polymerase chain reaction Koch's bacillus in gastric fluid and urine) was negative, as well as interferon gamma release assay (IGRA), hepatitis A, B, and C, and HIV. Blood gas analysis, including ionised calcium and vitamins B3, B6 and B12 were in the normal range. An immune study showed low levels of IgG and IgA, with normal complement and lymphocyte populations. Cow's milk protein allergy investigation (by specific radioallergosorbent test (RAST)) was negative, as well as stool cultures, and parasite and viral studies (table 1).

Because of a persistent and refractory dermatitis, a cutaneous biopsy of the abdominal area was performed, showing unspecific features such as: neutrophil focal parakeratoses, decreased stratum granulosum and sparse lymphohistiocytic perivascular infiltrate. Considering the infant's history and clinical features, a zinc assay was requested. Infant serum zinc level was low 33 µg/dL (RR >60 µg/dL), with normal albumin levels, confirming the zinc deficit. A zinc study in the mother was requested, revelling very low levels in breast milk (270µg/L; RR 1000–2500 µg/L) with normal plasma zinc levels (111.3 µg/dL; RR 68–120 µg/dL). These findings raised the suspicion of TSZD due to decreased excretion in breast milk. Genetic study of SLC39A4 was not performed.

DIFFERENTIAL DIAGNOSIS

The first assumed diagnostic was generalised eczema because it is the most frequent cause of dermatitis in this age group. The presence of a pruritic erythematous scaling rash, reaching the cervical and axillar areas, was suggestive of atopic dermatitis. However, there was no response to corticosteroids. Seborrhoeic dermatitis is a common dermatosis in young infants. It is usually characterised as a greasy, scaly dermatitis, and rarely as erythrodermic. Although the affected areas could be similar to our case, the lesions on the scalp and nasolabial folds should be different, with red, crusted and yellow scaling plates. Lesions are usually asymptomatic and responsive to corticosteroid therapy, making this hypothesis less probable.

Table 1 Laboratory evaluation

Diagnostic test	Result	Diagostic test	Result
Haemoglobin (RR 9.5–13.5 g/dL)	10.9	B12 vitamin (RR 211–911 pg/mL)	427
Haematocrit (RR 29–41%)	30.8	B6 vitamin (RR 23–172.5 nmol/L)	90.3
Leucocytes (×10^3/µL)	14.6	B3 vitamin (RR 8–52 µg/L)	10
Neutrophils (×10^3/µL)	3.36	Complement C3 fraction (RR 90–180 mg/dL)	99.9
Eosinophils (×10^3/µL)	0.55	Complement C4 fraction (RR 10–40 mg/dL)	15.6
Basophils (×10^3/µL)	0.03	CH50 activity (RR >24 U/mL)	58.6
Lymphocytes (×10^3/µL)	9.23	IgA (RR 27–86 mg/dL)	<23.7
Monocytes (×10^3/µL)	1.48	IgG (RR: 335–623 mg/dL)	224.39
Platelets (RR 150–400×10^3/µL)	580	IgM (RR 48–136 mg/dL)	64.64
C reactive protein (RR 0.06–1.0 mg/dL)	<0.50	Total IgE (RR <3.8 UI/ml)	3.24
Erythrocyte sedimentation rate (RR <10 mm/h)	13	RAST alfa lactoalbumin	Undetectable
Alkaline phosphatase (RR 125–449 UI/L)	251	RAST beta lactoalbumin	Undetectable
Creatinine (RR 0.2–0.5 mg/dL)	0.3	RAST casein	Undetectable
Nitrogen urea (RR 12.8–36.4 mg/dL)	12	HBe antibody	Undetectable
Aminotransferase aspartate (RR 16–60 IU/L)	39	HBs antibody	Reactive
Aminotransferase alanine (RR 26–51 UI/L)	32	HBs antigen	Non-reactive
Sodium (RR 132–140 mmol/L)	138	HCV antibody	Undetectable
Potassium (RR 3,5–5,8 mmol/L)	4.5	HAV antibody	Undetectable
Zinc (RR >60 µg/dL)	33	HIV 1,2 antibody	Undetectable
Albumin (RR 2.3–4.4 g/dL)	3.49	IGRA	Negative

CH50, Total hemolytic complement; HAV, hepatitis A virus; HBe, hepatitis B e; HBs, hepatitis B s antigen; HCV, hepatitis C virus; HIV, Human Immunodefency virus ; Ig, immunoglobulin; IGRA, interferon gamma release assay; RAST, radioallergosorbent test; RR, reference range.

Considering exclusive breastfeeding by a mother who was treated with isoniazid, toxidermia was also hypothesised. Cutaneous hypersensitivity reactions are more likely to present has maculopapular or urticariform rash. Other forms are usually of greater severity (eg, fever) and involve other systems. Isoniazid is excreted into breast milk in a non-significant amount and there was no improvement after the mother stopped treatment, making this diagnosis unlikely.

Other disorders can cause skin lesions which resemble zinc deficiency, such as rare metabolic diseases (eg, methylmalonic acidaemia, propionic acidaemia, biotin deficiency, urea cycle disturbances or essential fatty disorders)[1 3 5 6] and neonatal lupus erythematosus. However, most have other clinical and laboratory findings.

Because zinc deficiency affects many aspects of the immune system, essentially the development and function of innate and acquired immune cells, phagocytosis and cytokine production, these patients can present with overlapping features of immunodeficiencies.

TREATMENT

Treatment with flucloxacillin was suspended after 5 days without any improvement. Systemic prednisolone was stopped after 24 hours, and topical hydrocortisone and ketoconazole was started. On the seventh day of treatment, the lesions remained equal and topical products were suspended. At that point, the diagnosis of zinc deficiency had been stablished, and oral zinc supplementation (zinc acetate) was started at 3 mg/kg/day, until the age of 6 months.

OUTCOME AND FOLLOW-UP

After zinc supplementation had been started, the infant showed progressive improvement of the erythematous rash during the first week, with complete resolution 1 month later. On discharge, 1 week after supplementation, at 4 months old, she had a weight gain of around 100 g (4380 g, CDC curves <P3) and at 5 months she weighed 5255 g (CDC curves P3), presenting good weight progression. Exclusive breastfeeding was maintained. Food diversification was started at the age of 5 months and zinc supplementation was suspended 1 month later with no relapse. At the age of 9 months, no symptoms were detected, and plasma zinc levels normalised. She was followed until 2 years of age. No relapses were observed, and the infant had adequate development and growth.

Based on clinical and laboratory features, as well as low zinc levels in the mother's milk, clinical remission after zinc supplementation and no relapses after weaning, the diagnosis of TSZD was assumed, and the genetic test was not performed.

DISCUSSION

Zinc is an essential trace element and its intake is closely related to protein intake, which makes it an important component of nutritionally related morbidity worldwide. Zinc is the second most common micronutrient after iron, being an intrinsic metal component or activating cofactor for more than 70 important enzymes systems, including DNA and RNA polymerase, carbonic anhydrase, alkaline phosphatases, dehydrogenases and carboxypeptidases.[1] It is involved in the regulation of nucleoproteins and the activity of various inflammatory cells, immune response and response to infection, and plays a role in growth, tissue repair and wound healing,[5] making these tissues particular susceptible to zinc deficiency. Consequently, numerous functions in humans are affected by zinc deficiency, particularly during periods of increased metabolism. Zinc levels are regulated by two transporter families, ZnT (SCL30) and Zip (SCL39), which have opposite functions and are expressed in different tissues.[1–3] ZnT1 protein is expressed in the small intestine, transferring zinc from the enterocyte to the bloodstream. Zip4 protein is expressed in enterocytes, increasing cytoplasmatic zinc concentrations. A third protein, ZnT2, is found in high concentrations in the mammary gland, regulating zinc transfer to human milk.[3]

Most of the literature on zinc deficiency is made up of reports and reviews about the rare hereditary form of acrodermatitis enteropathica, which results form loss-of-function mutations in SLC39A4 gene (Zip4).[2 4 7 8] However, acquired forms of zinc deficiency are significantly more frequent, with an increasing number of case reports published in the last decades, illustrating that medical community is more aware of this condition.

TSZD is a type of acquired neonatal hypozincaemia that occurs in exclusively breastfed infants.[4] An inadequate zinc level in human milk, despite normal serum zinc levels in the mother, is caused by decreased breast milk zinc secretion, classically associated with mutations in the SLC30A2 gene that encodes the ZnT2 zinc transporter.[9] Premature and/or very low birth weight infants are more susceptible.[3 9] In this population, high requirements for growth and environmental injuries, physiological intestinal insufficiency and frequent use of antibiotics, significantly increase the risk of zinc deficiency. In addition, preterm birth reduces the duration of pregnancy, with most of fetal zinc accretion occurring after the 24th week of gestation (in the last trimester, the mother transfers to the fetus up to 1.5 mg/kg of zinc every day) and thus the amount of hepatic stores available during periods of reduced zinc intake.[10]

Apart from TNZD, there are a large number of conditions that can lead to acquired hypozincaemia, acting by increasing loss or requirement, or decreasing intestinal absorption.[1 11 12] The classic triad of acral and periorificial dermatitis, alopecia and diarrhoea is characteristic of zinc deficiency and can occur regardless of the underlying cause. Because zinc assumes several functions, clinical manifestations of its deficit can be varied: irritability, paronychia, impaired wound healing, glossitis, dysgeusia, dysosmia, cognitive impairment and increased incidence of infections.[1 4 9]

Failure to thrive and growth retardation can also be found in infants and children. The literature reports the classic triad in a third of patients.[6 13] In our case, only acral and periorificial dermatitis of the classic symptoms were present, but irritability and failure to thrive were found. Clinical suspicion was determined by the lack of response to antibiotics and steroids therapy and by the type of skin lesions. Low serum zinc levels confirmed the diagnosis. It is important to note that plasma contains only 0.1% of the body's zinc[14] and laboratory tests have low sensitivity. Therefore, infants with possible acrodermatitis can be responsive to zinc supplementation, regardless of normal zinc values in plasma. In exclusively breastfed infants, zinc should be measured in the mother's milk and, similar to our patient, it can be low confirming the diagnosis of TNDZ.

In addition to serum zinc levels, zinc dependent enzymes, such as alkaline phosphatase,[1] are often decreased in this condition and can be useful in supporting the diagnosis.[11] Our patient had normal alkaline phosphatase.

When classic symptoms are present, the diagnosis should be easier. With incomplete or atypical clinical manifestations, the cutaneous biopsy can be useful. Histology in zinc deficiency is non-specific and usually indistinguishable from other diseases, such as cutaneous manifestations of metabolic disorders.[1] In more advanced stages of the disease, the presence of ballooning degeneration of keratinocytes is a common histological finding.[1]

Learning points

- Zinc deficiency in paediatric patients is caused by different mechanisms and conditions.
- Zinc deficiency is a multisystemic disorder, usually described by the classic triad of acral and periorificial dermatitis, alopecia and diarrhoea, which may be incomplete.
- Some groups, such as preterm or low birth weight infants, are predisposed to symptomatic zinc deficiency.
- Mutations in the maternal SLC20A2/ZnT2 gene reduce zinc excretion in human milk and can predispose to transient symptomatic zinc deficiency.
- Zinc deficiency, in particular the acquired forms, is an under recognised condition and is easily treated.

Histological findings do not usually allow the diagnosis to be established but it helped exclude other forms of dermatitis. However, findings such as neutrophil focal parakeratoses, decreased stratum granulosum and sparse lymphohistiocytic perivascular infiltrate were described by some authors as part of the continuous modifications during the process of the disease if no treatment is started.[1]

Oral zinc supplementation is the recommended treatment, determined by the underlying cause. The daily dose of elemental zinc varies between 0.5 and 1 mg/kg/day for patients with acquired forms, and 3 mg/kg/day for acrodermatitis enteropathica.[1 3] Dosages may be adjusted according to measurements, every 3–6 months.[13] While acrodermatitis enteropathica needs lifelong supplementation, in TSZD, replacement therapy must be kept until food diversification is established and serum zinc levels are found within the reference range. Usually, clinical improvement by supplementation therapy is observed after a few days to weeks, but some reviews point to response rates of up to 70% in the first 6 months of treatment.[14] Therefore, clinical remission with zinc supplementation remains the best diagnostic tool.

The subtle clinical features of zinc deficiency make it difficult to recognise. High suspicion is needed in infants with persistent typical dermatitis, particularly if exclusively breastfed, and belonging to populations at risk. Depending on the underlying cause, cooperation between different specialties (paediatricians, dermatologists and gastroenterologists) might be advantageous.

Contributors MC: conceptualisation, writing original draft and scientific review. MCS: review and editing the manuscript, and scientific review. ET: scientific review and review of the manuscript. FC: supervision, review of the manuscript and conceptualisation.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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