Acrodermatitis enteropathica during parenteral nutrition: a pediatric case report

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Research Article

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Abstract

**Background:** Acrodermatitis enteropathica is a rare disorder characterized by the triad composed by dermatitis, alopecia and diarrhoea. Its acquired form can be caused by inadequate zinc intake, malabsorptive processes, excessive renal or intestinal loss. A rare cause of acquired zinc deficiency is iatrogenic nutritional deficiency due to parenteral nutrition.

The diagnosis can be really difficult because the early clinical signs are non-specific and patient’s eventual comorbidities can often mask symptoms.

**Case presentation:** A 5-years-old child affected by several comorbidities, consequent to *C. Koseri* meningo-encephalitis occurred in the neonatal period, was admitted to Pediatric ward for acute pancreatitis and he had been fed via total parenteral nutrition for one month. Symptoms started approximately 15 days after the start of a standardised standardized parenteral nutrition mixture. The child presented with diarrhoea, alopecia and erythematous bullous skin lesions, distributed predominantly in acral and periorificial sites and not responsive to topical treatments. Zinc serum dosage were very low (10 µg/dL, with normal values 68-107 µg/dL). Clinical improvement was very fast after oral zinc supplementation (5mg/daily), with a rapid regularisation in the intestinal habits and re-epithelialization of the skin lesions.

**Conclusion:** Trace elements are an essential component of parenteral nutrition. The supplementation of trace elements is a complex and important part of the parenteral nutrition prescription. Even few days of zinc shortage, especially in frail patients, may cause a severe dermatitis that can be easily prevented. Despite its rarity, acrodermatitis enteropathica should be strongly considered in the differential diagnosis of skin lesions for these patients.

Background

Acrodermatitis enteropathica (AE) is a rare disorder caused by zinc deficiency characterized by the triad: dermatitis, alopecia and diarrhoea [1]. AE can be congenital, more common in infants during the first period of life, or acquired. Congenital form is due to an autosomal recessive mutation in the gene SLC39A4 [1]. This gene, located in chromosome 8q24.3, codifies for the zinc-ligand binding protein (Zip4), which is expressed in duodenum and jejunum and its mutation reduces the intestinal absorption of zinc [2]. Over 30 mutations of the responsible gene have currently been reported [3].

Acquired AE can be caused by a lot of causes: inadequate zinc intake, excessive renal or intestinal loss, malignancy, drugs, ethanol, pregnancy, malnutrition, high-fibre diet or malabsorption syndromes, such as cystic fibrosis [4] [5].

Rare cause of acquired zinc deficiency is an iatrogenic nutritional deficiency caused by total parenteral nutrition (PN).
AE early clinical signs are nonspecific and they can also mimic common dermatoses, particularly atopic dermatitis and, therefore, often lead to a delay in diagnosis and treatment [5].

We describe the challenge AE diagnosis in a pediatric patient with several comorbidities, and report a complete diagnostic workflow for pediatric patients with chronic complex conditions.

**Case Presentation**

A 5-years-old child, with a chronic complex condition affected by several comorbidities, including spastic tetraparesis, focal epilepsy, tetraventricular hydrocephalus, severe blindness and intellectual disability, consequent to *C. Koseri* meningoencephalitis occurred in the neonatal period, was admitted to Pediatric ward for acute pancreatitis. On admission patient clinical condition was fair and enteral nutrition via nasal feeding tube was started. Due to the worsening of septic conditions and to increasing respiratory requirement, on hospital day 5, total PN was initiated. A standardised PN mixture (Numeta G13%) was prescribed via a central line [6]. Numeta G13% is formulated to follow the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and The European Society of Clinical Nutrition and Metabolism (ESPEN) guidelines to meet pediatric nutritional needs with a balanced formulation of amino acids (protein), glucose (carbohydrates), lipids (fats) and electrolytes [7]. In the presumption that the patient would be on PN for a short period of time, the trace elements (TE) package was not added to the bag. Otherwise, he remained on total PN for approximately 4 weeks as his only source of nutrition, due his increased risk of aspiration, and an elevated lipase (600-1000 µ/L), concerning for pancreatitis.

After approximately 15 days on total PN, he developed diarrhea and skin lesions (Fig. 1). The lesions were, at the beginning, macules involving cheeks, hands and foot fingers and ears. Within a few days the eruption involved perianal and perineal regions and evolving into large tense bullae and then into scaly plaques and ulcerations. The lesions were surrounded by healthy skin. In addition, the child presented with diffuse alopecia. On physical examination the patient was painful and irritable.

Skin lesions were first treated with topical antibiotics agents (Gentamicin) and steroids (Betamethasone) without improvement. All cutaneous swab resulted negative for bacterial or mycotic infections.

He received intravenous antibiotic treatment (Vancomycin and Cefepime) with improvement of his clinical general condition, but no improvement was observed for skin lesions.

Patient underwent two dermatological evaluations that suggested additional laboratory studies. Zinc dosage was found very low (10 µg/dl with normal values 68–107 µg/dl). Thus, suspecting acquired AE, an oral zinc supplementation was initiated in the amount of 5 mg daily, i.e. the highest one according to ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals [8].

Clinical improvement was very fast. After only 4 days of oral supplementation, a rapid regularisation in the intestinal habits and re-epithelialization of the skin lesions were noticed. Patient was discharged after 42 days of hospitalisation in good clinical condition.
He returned for clinical control after 32 days of treatment: skin lesions showed complete resolution, with total *restitutio ad integrum* of the skin.

**Discussion And Conclusions**

Zinc is an essential micronutrient obtained from diet. About 17% of the world's human population suffers from zinc deficiency [9]. It is more prevalent in areas of high cereal and low animal food consumption [10].

The roles of zinc in biology can be grouped into three categories: catalytic, structural and regulatory functions [10]. It has a recognized action on more than 300 enzymes by participating in their structure or in their catalytic and regulatory actions [11]. Therefore, zinc is essential for the proper working of various organs and systems, from the gastro-intestinal tract to the central nervous system. In the human body, zinc is stably maintained in the weight of 2–3 g [12].

Skin is the third most zinc-abundant tissue in our body (skeletal muscle 60%, bones 30%, liver 5%, and skin 5%) [13]. It is involved in epidermal keratinocyte differentiation and growth as well as in anti-inflammatory processes and wound healing [14] and is crucial for epidermal stem cells [15]. Knowing its roles, it's clear that a zinc deficiency can cause various clinical manifestations, which can involve every organ and system.

Zinc deficiency can be inherited or acquired. -Risk populations for the acquired one include breast-fed premature infants, exclusively cow's milk fed infants, patients with renal disease, malabsorption due to Crohn disease and cystic fibrosis, and others. An under-recognized risk-group is represented by PN fed patients, without adequate zinc supplementation [16].

AE, a clinical condition characterized by the triad composed by acral and periorificial dermatitis, alopecia and diarrhea, was firstly reported in 1936 by Brandt, who described a dermatitis in children with disturbances of the general condition and the absorption of food elements [17], but it was later identified as a distinct disease by Danbolt and Closs, in 1942 [18].

AE's classic clinical manifestations are flanked by other symptoms, such as paronychia, onicodistrophy, angular stomatitis, cheilitis, conjunctivitis and photophobia [2]. Skin manifestations predominate and are characterized by asymptomatic, sharply demarcated eczematous plaques with peripheral scaling and crust. These lesions are localized in an acral, periorificial (sparing the upper lip) and anogenital regions. Fingers and toes may also be involved, along with symmetrical involvement of the extensor surfaces of elbows, knees, hands, and feet.

In clinical practice it is not infrequent to face with patients who have an incomplete diet or are already defied when hospitalization happens.

When these patients need PN, the most frequent choice is to use as a standard, commercial, formulation [7]. These are safely prepared to meet the need of patients of similar age and clinical conditions, but do
not necessarily meet all their nutritional requirements, even more in case of long-term parenteral nutrition (i.e. > 3 months long) [19]

Alternatively, an individually tailored PN formulation, adapted to the patient's nutritional needs, can be prescribed. As for standard PN, it may be lacking in trace elements. Moreover, the role of TE is not often known or takes a back seat during hospitalization for acute severe illnesses, even if they are essential to support normal physiological processes. Their lack can lead to the so called “hidden hunger”, which is the presence of multiple micronutrient deficiencies (particularly iron, zinc, iodine and vitamin A), that can occur without a deficit in energy intake [20]. In current practice there is not a consensus in TE prescription, and, for paediatric patients, it requires age related dosing [21]. Focusing on zinc, children with hypercatabolism have high zinc requirements due to elevated losses. As standard PN contain fixed zinc dose, additional zinc should be added. Current recommendations are to supply 400–500 mg/kg/d in preterm infants, 250 mg/kg/d in infants from term to 3 months, 100 mg/kg per day for infants from 3 to 12 months and 50 mg/kg/d in children > 12 months of age (up to a maximum of 5 mg/d for routine supplementation) [8]. Zinc status (serum Zn, alkaline phosphatase) should be periodically monitored in patients on long-term PN and more often in those who may have significantly higher Zinc requirements [8].

Heading back to our patient, he is a child with previous malnutrition, linked to the family's willingness to continue a feeding by mouth by refusing the placement of a percutaneous endoscopic gastrostomy, with weight and height growth delay. His several comorbidities, pancreatitis, sepsis and consequent multiple pharmacological treatments on-going made the diagnosis difficult.

This case underlines the importance of TE integration during PN, because zinc deficiency can occur quickly, even after few days, especially in defied and high energy requiring patients. Current guidelines suggest to supplement different amounts of zinc based on the patient's age. Our case shows how this rule may not always be valid. In fact, the patient was 5 years old, with anthropometric parameters corresponding to the average ones of 1-year-old child. Moreover, his comorbidities and special nutritional needs may exacerbate the clinical effects of iatrogenic zinc deficiency. Clinical clues of AE must be well known and TE dosage must be undergone in a patient under PN to detect and treat any deficit. Adequate monitoring of the metabolic and nutritional status of an infant on standardized PN should be assured. Individually tailored PN solution should generally be used when the nutritional needs cannot be met by the available range of standard PN formulations (i.e. in very sick and metabolically unstable patients such as those with abnormal fluid and electrolyte losses) [7].

In conclusion, the supplementation of TE is a complex and important part of the PN prescription. Even few days of zinc shortage, especially in frail patients, may cause a severe dermatitis that can be easily prevented. Considering this, a patient-tailored zinc integration must be evaluated. In frail children, a zinc baseline followed by multiple dosages on a regular basis, even if in a short term PN, must be considered.

Abbreviations
AE: Acrodermatitis enteropathica

PN: Parenteral Nutrition

TE: Trace Elements

Declarations

Conflict of Interest. The authors declare that they have no competing interests.

Ethics approval and consent to participate. Not required.

Consent for publication. Written informed consent was obtained from the patient’s legal guardian for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief.

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References


**Figures**
Figure 1

Patient's acrodermatitis