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CLINICAL STUDY

Extremely rare complication in high-risk newborn on long-term parenteral nutrition and large stool losses through ileostomy

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ABSTRACT
AIM: To analyse postnatal characteristics, clinical and laboratory findings, results of investigations in the newborn (25 gestational weeks; Apgar score: 6/9 points; born per caesarean section; birth weight: 600 g; birth length: 31 cm; head circumference: 21 cm) from the first high-risk pregnancy with acquired form of acrodermatitis enteropathica.
RESULTS: After summarizing the clinical picture with laboratory findings, we analysed the components of parenteral nutrition with regard to the deficiency of trace elements and vitamins. The zinc depletion dominated.
CONCLUSION: The diagnosis is clinical, based on the presence of a typical clinical picture together with a low serum zinc concentration. Standard preparations with elementary elements do not sufficiently cover the daily needs of children, other possibilities of supplementation in intravenous form are not available. It is necessary to supplement zinc in premature children, in children with high losses of zinc (with diarrhoea, in patients with a stoma, in patients with severe skin disease) *(Fig. 4, Ref. 15)*. Text in PDF www.elis.sk
KEY WORDS: newborn, zinc, trace elements, acrodermatitis enteropathica.

Abbreviations: Zn – zinc, ALP – alkaline phosphatase

Introduction

Acrodermatitis enteropathica occurs in two forms, hereditary (primary acrodermatitis enteropathica) or acquired. The difference is in the aetiology of the disease, where in the hereditary form it is an autosomal recessive disease caused by a mutation of the SLC39A4 gene, which is responsible for coding the ZIP4 zinc (Zn) transporter in the organism. Whereas the acquired form of the disease is caused by a disorder in the supply and demand of Zn in the body. The symptoms of these forms of the disease do not differ significantly, in both cases there is a progressive improvement with adequate supplementation. The difference occurs after the end of supplementation, in the case of the hereditary form, the disease relapses when the supplementation ends, in the case of the acquired form of acrodermatitis enteropathica, relapse does not occur under adequate conditions. The hereditary form of the disease is determined only by the final genetic examination, in the acquired form we speak of a clinical diagnosis, which is based on objective and laboratory findings with an adequate response to treatment (1, 2, 3).

The symptoms of the disease are varied. There is a triad of symptoms: typical localization (perioral, acral, perianal dermatitis), steatorrhea and alopecia. Although this triad of symptoms is considered typical, it occurred in only about 1/3 of cases in the available case reports. Other manifestations of the disease include: delayed wound healing, eroded squamous eruptions, crusts, vesiculobullous lesions, local necrosis, inflamed nail beds, slowed growth, higher risk of infections and neurological disorders (1, 4).

The diagnosis of the disease is based on a physical examination, culture examinations from the affected areas, biochemical parameters, urinalysis, biopsy, and ultimately genetic examination. In exclusively breast-fed premature infants with typical symptoms, an examination of Zn concentration in breast milk and maternal serum should be considered. A mutation of the gene responsible for the transfer of Zn into breast milk may be present in the mother, after ruling out a dietary error (1, 4). Contact dermatitis, impetigo, candidiasis, mycotic infections – filamentous fungi, immunosuppression – wound dehiscence, secondary infection must be excluded in the differential diagnosis.

Case report

This was an extremely immature newborn (25 gestational weeks; Apgar score was 6/9 points), female, from the first high-

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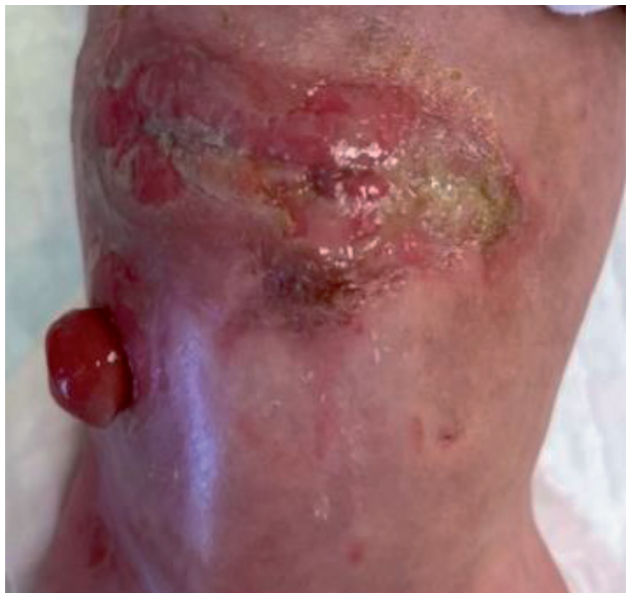

Fig. 1a. Before treatment with Zinc.

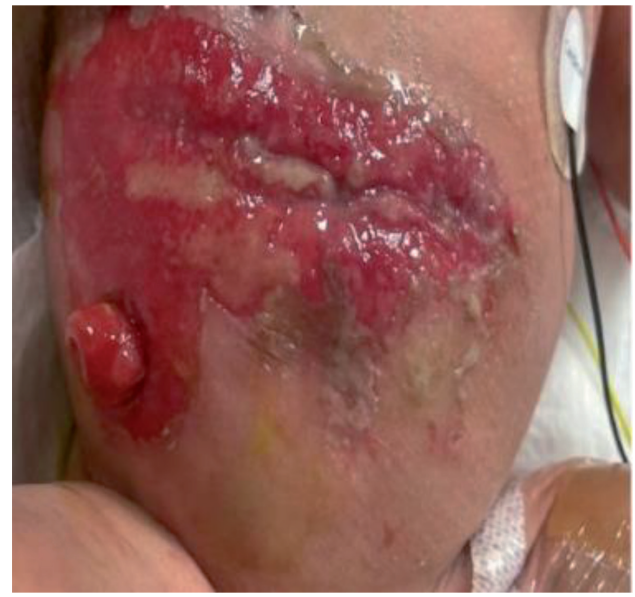

Fig. 1b. Skin changes after 1day of supplementation of Zinc.

risk pregnancy, born per sectionem caesarean, in a mother with premature outflow of amniotic fluid (35 days) and elevation of inflammatory markers. Birth weight was 600g (>10th percentile according to Intergrowth 21), birth length 31cm (>10th percentile according to Intergrowth 21), head circumference 21 cm (>50th percentile according to Intergrowth 21). Clinical signs of respiratory distress syndrome required a distension ventilatory support which was changed to artificial lung ventilation with Surfactant application (200 mg/kg intratracheally). Hypotension and support of microcirculation required inotropic support. Due to the positive family history from the mother's point of view empiric antibiotic therapy was given. The trophic feeding (pasteurized human milk) began on the 3rd day of life. Clinical condition was on the 8th day of age altered by pneumoperitoneum.

The newborn was admitted to our department on the 8th day of age (weight: 680 g; on artificial pulmonary ventilation; oxygen therapy up to 25%). The newborn underwent surgical revision under general anaesthesia with suturing of the terminal ileostomy. Postoperative management was complicated by severe lung involvement. Due to the increasing dependence on oxygen therapy up to 60% and hypercapnia, the condition required change to high-frequency ventilation for 4 days. Due to the X-ray finding of lung involvement, we performed a bronchoalveolar lavage examination, which was negative for microorganisms causing atypical pneumonia, but cytomegalovirus pneumonitis was confirmed in the newborn. The child was treated with an antiviral for 6 weeks until the result of the virus copy in the urine was negative. Severe bronchopulmonary dysplasia has developed.

During hospitalization, the child underwent 2 more laparotomies due to complications from the alimentary tract (postoperative development of necrotizing enterocolitis with pneumoperitoneum; revision for developed stercoral peritonitis due to leakage of intestinal contents during dehiscence at the site of the original anastomosis). She underwent intravitreal application of anti-growth factors due to development of retinopathy of prematurity.

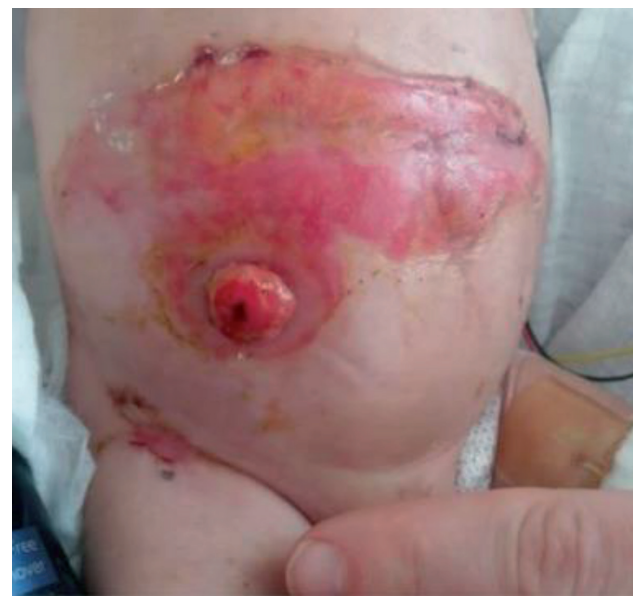

Fig. 1c. Skin changes on 3rd day after supplementation of Zinc.

After the aforementioned surgical revisions, the postoperative course was without serious complications, the child was gradually refed with pasteurized breast milk in order to supplement macronutrients and increase caloric intake with protein supplementation. On the 54th day of hospitalization (on the 62nd day of age), the child achieved full enteral intake. She was thriving with a double increase in birth weight (1206 g) and was transferred to the district hospital.

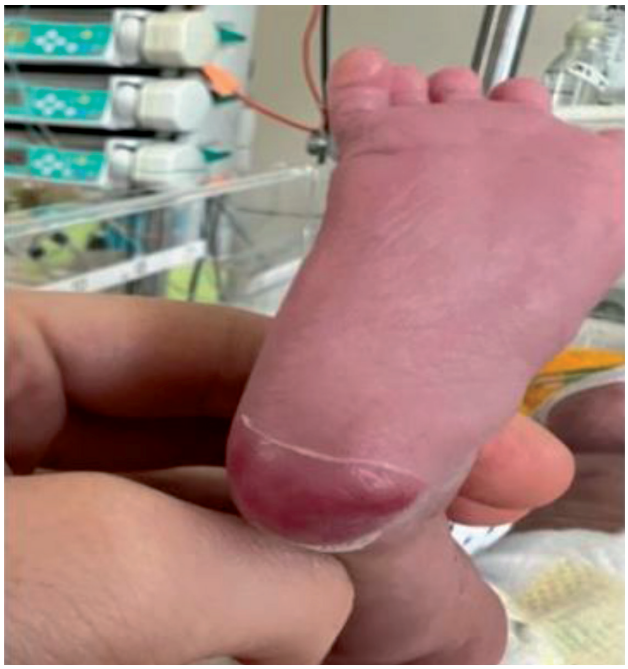

Fig. 2a. Skin desquamation before treatment.

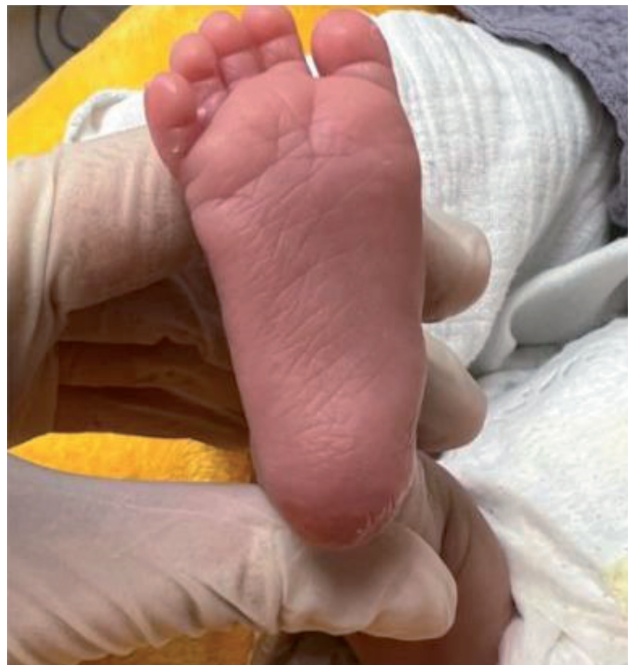

Fig. 2b. Skin desquamation on 10th day after supplementation of Zinc.

The child had to be re-hospitalized for developed necrotizing enterocolitis IIA according to Bell at our department after 3 days (weight 1280 g). On admission, the child was in severe clinical condition, dehydrated, with high blood waste through the ileostomy (positive antigens of astroviruses and adenoviruses) occurring under the described clinical picture. After this infectious insult, we refed the child according to the recommendations of the paediatric gastroenterologist. Enteral tolerance threshold was not achieved in the child. The patient was dependent on total parenteral nutrition, with daily replacement of vitamins and trace elements. Secondary malabsorption developed with high ileostomy losses. The mass curve had a stagnant character. Based on the analysis of the volume of ileostomy waste, it could be said that as long as the child was without enteral intake, the volume of waste from the ileostomy was reduced. The burden of the digestive tract with artificial milk formula based on amino acids, rice decoction, full physiological solution in trophic doses (8x1–2 ml) caused progressive loss of fluids through the stoma.

The child was cardiorespiratory stabilized, connected to high-frequency nasal cannula, with the need for an oxygen fraction of up to 25% in the 37th corrected week of the child's age (on the 35th day of rehospitalization). Set up for total parenteral nutrition with daily replacement of vitamins and trace elements (total fluids 150ml/kg/day, total proteins 4 g/kg, total sugars 15 g/kg, total fats 4.5 g/kg). In the objective findings, a dehiscence of the surgical wound appeared, a day later with the progression of the skin findings in the sense of maceration around the perimeter of the surgical wound, with the association of other pathological skin efflorescences, namely crusts, eroded squamous eruptions perinasal, perioral, necrosis and peeling of the epidermis of the hands and feet, alopecia (Figs 1a, 1b, 1c, 2a, 2b, 3a, 3b, 4a, 4b). Based on the results of the laboratory tests, we modified the therapy. Due to hypochromic anaemia, we replenished the red blood component by administering a blood transfusion, in the case of thrombocytopaenia and a serious clinical condition, we administered thrombo-concentrate to the child. For secondary immunodeficiency in hypogammaglobulinemia, we added immunoglobulin G, increased the substitution of ascorbic acid in supramaximal doses (250 mg/kg/day). The child was treated with antibiotics (Tazocin monotherapy) due to the dehiscence of the surgical wound and immunodeficiency. In case of high losses due to ileostomy and hypoalbuminemia, we supplemented daily with 20% albumin at a dose of 1g/kg intravenously. Based on the laboratory results, secondary malabsorption with malnutrition was confirmed in the patient. Culture examination of the tonsils, nose, rectum, surgical wound and affected sites were negative. The blood culture taken from the peripheral blood and the central venous catheter were negative for aerobic, anaerobic and fungal microorganisms.

After summarizing the clinical picture with laboratory findings, we analysed the components of parenteral nutrition with regard to the deficiency of trace elements and vitamins. The Zn depletion dominated (5, 6). It was shown that despite the daily substitution of micronutrients in the recommended doses, we did not reach the recommended values of the child's daily need for trace elements and vitamins, in addition, our patient also had enteral losses through the stoma (5, 7, 8, 9). The recommended value of the intravenous form of Zn in a premature newborn is 400-500 µg/kg/day, based on the recommended dosage of the solution of trace elements (Addaven 0.1 ml/kg), our patient

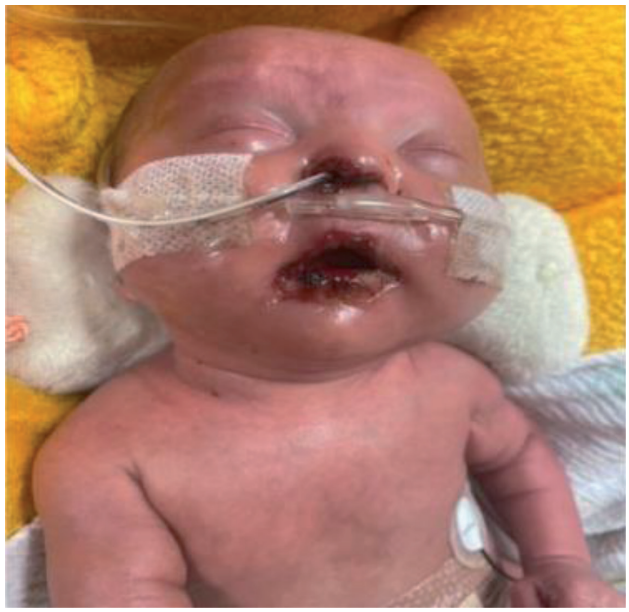

Fig. 3a. Skin efflorescences around the mouth and the nose before treatment.

Fig. 3b. Skin efflorescences around the mouth and the nose on 10th day after supplementation of Zinc.

reached only 11% of the recommended daily dose of 50 µg/kg/day (7, 10, 11, 12).

On the 1st day of symptoms, the serum Zn concentration was 1.2 µmol/l (Zn reference values 11–22 µmol/l), the alkaline phosphatase (ALP) concentration was also significantly below the lower limit of the norm (ALP 0.22 µkat/l). Basic laboratory parameters of bone metabolism were satisfactory. Due to a significant Zn deficiency, we applied local therapy (Fucidine ointment, 1% lactic acid, Erevit) to the pathological skin deposits and increased Zn administration in both oral and intravenous form. In increasing the dose in intravenous form, we were limited by the concentration of other trace elements in the available pharmacological preparation of trace elements. The regression of the pathological skin efflorescences in the child was visible already on the 3rd day after correction of the treatment (Fig. 1c). We reached Zn concentration at the lower limit of the reference value (Zn 11.4 µmol/l) and the value of ALP was adjusted to normal on the 7th day of treatment. Normoalbuminaemia during albumin substitution was maintained. We were able to gradually deescalate the high doses of Zn doses.

Discussion

Zinc is an essential trace element (13, 14). It contributes to growth, it is a part of the immune, nervous and endocrine systems. It is represented by 60% in skeletal muscle, 30% in bones and 5% in skin and liver. The recommended dosage of Zn for newborns on total parenteral nutrition according to ESPHGAN 2018 is as follows: 400–500 µg/kg/day for premature newborns, 250 µg/kg/day for full-term newborns up to 3 months of age, 100 µg/kg/day for full-term newborns from 3–12 months of age (5, 9).

Control of the Zn status (Zn, ALP in the serum) is recommended periodically in children on parenteral nutrition (10). More often with high losses of enteral fluids. In infants on total parenteral nutrition, Zn is excreted through urine and enteral losses.

The concentration of alkaline phosphatase and albumin must be mentioned in Zn depletion. These two parameters can help us to detect a possible Zn deficiency at a time when the clinical picture described above occurs in the differential diagnosis. Zn is a cofactor of alkaline phosphatase and 80% of Zn in the body is bound to albumin.

There is no clear consensus about the dose of Zn supplementation. Different dosage schemes are presented. The general recommendation for Zn deficiency and acrodermatitis enteropathica is to administer initially 3 mg/kg every 8–12 hours orally. The dose must be titrated to reach a serum Zn concentration of 11–22 µmol/l. For diarrhoea, the recommended dosage is 10-20 mg/day orally (6, 15). Other authors recommend an initial oral dose of 5 mg/kg/day (2). According to ESPHGAN 2018, AuSPEN 2021, the dose of Zn for a premature newborn on total parenteral nutrition is 400–500 µg/kg/day intravenously (5, 9).

The Zn toxicity is rare, side effects of overdose include nausea, vomiting, loss of appetite, abdominal pain, diarrhoea. When administering high doses of Zn over a long period of time, it is necessary to think about possible interaction with the absorption of copper. Copper and Zn act as antagonists in the body. The function of iron in the body can also be affected (7, 8).

Addaven, a pharmacological preparation of trace elements available on the market, which we also gave to our patient, has a recommended dosage for children with a body weight of <15 kg: 0.1 ml/kg/day, the maximum dose is 10 ml/day. The recommended dose of the intravenous form of Zn in a premature

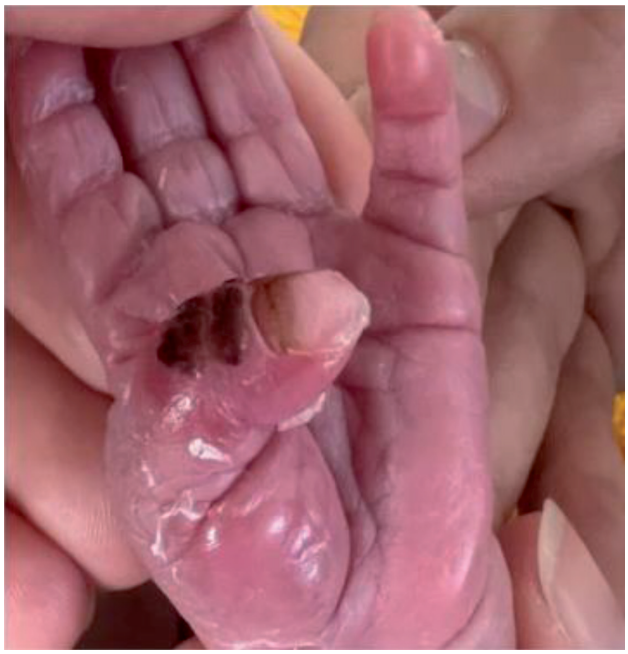

Fig. 4a. Skin efflorescences on the left thumb before treatment.

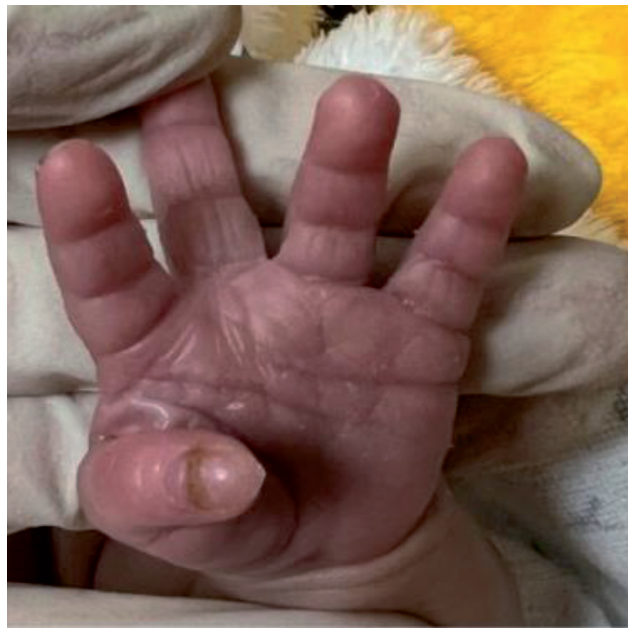

Fig. 4b. Skin efflorescences on the left thumb on 10th day after supplementation of Zinc.

newborn is 400–500 µg/kg/day, but in order to achieve an optimal concentration of Zn, we were limited by the presence of a high concentration of magnesium in the preparation. The maximum dose of magnesium should be <1 µg/kg/day, if this amount is exceeded and overdose, neurotoxicity may develop. Magnesium is considered a trace element solution contaminant. Moreover, in newborns on long-term parenteral nutrition, there is a risk of developing cholestasis associated with total parenteral nutrition. In this case, it is recommended to administer trace elements, mainly magnesium and copper, twice a week due to the risk of biliary obstruction (11, 12).

Conclusion

Acquired acrodermatitis enteropathica is a rare but potentially life-threatening disease. It is characterized by a triad of symptoms of perioral, acral, perianal dermatitis, diarrhoea and alopecia. The diagnosis is clinical, based on the presence of a typical clinical picture together with a low serum Zn concentration. After supplementation there is a rapid regression of the disease manifestations. The recommended dosage of Zn is 3–5 mg/kg/day in oral form and 400–500 µg/kg/day intravenously in premature newborns (5, 9). Premature newborns need a higher intake of Zn for their accelerated growth (15). Regular monitoring of trace elements is necessary in children on long-term parenteral nutrition, especially in those who also have enteral losses. Standard preparations with elementary elements do not sufficiently cover the daily needs of children, other possibilities of supplementation in intravenous form are not available. It is necessary to supplement Zn in premature children, in children with high losses of Zn (with diarrhoea, in patients with a stoma, in patients with severe skin disease).

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