Relato de Caso

Current concepts in acrodermatitis enteropathica. Case report in a brazilian boy

Conceitos atuais em acrodermatite enteropática Relato de caso em menino brasileiro

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SUMMARY

Acrodermatitis enteropathica (AE) is a rare, recessively inherited disorder of zinc metabolism, which usually presents in infancy, at the time of weaning, with the triad alopecia, diarrhea and dermatitis with lesions of periorificial and acral distribution. We report a full-term 2-year-old boy with typical skin leions, decreased plasma zinc and alkaline phosphatase levels, that improved with zinc sulfate supplementation. He presented relapse of the symptoms and lesions when the medication was interrupted, in several occasions, suggesting treatment for long-life. A bried historial report and current genetics concepts are discussed. Currently, gene 8p24.3, SLC39A4, in the apical membrane of the enterocytes, was implicated in AE. In Brazil there are few reports of AE.

Keywords: Acrodermatitis enteropathica, dwermatitis, diarrhea, malabsorption, zinc.

RESUMO

Acrodermatitis enteropathica (AE) é um distúrbio recessivo raro do metabolismo do zinco que habitualmente se apresenta à época do desmame. A tríade característidca é alopecia, diarreia e dermatite com lesões periorificiais e de distribuição acral. Relata-se o caso de um menino de 2 anos de idade, nascido a termo, alimentado com leite de vaca, com lesões de pele típicas de AE, tendo níveis plasmáticos reduzidos de zinco e de fosfatase alcalina. A suplementação de zinco acarretou melhora do quadro, mas sintomas e lesões reapareceram quando a medicação foi interrompida, em diferentes épocas, sugerindo que deva ser continuada indefinidamente. Faz-se breve revisão histórica e dos conceitos genéticos atuais. Gene na região 8p24.3, SLC39A4, expresso na membrana apical dos enterócitos, está relacionado do com a AE. No Brasil há poucos relatos desta afecção.

Unitermos: Acrodermatitis enteropathica, dermatite, diarreia, mábsorção, zinco.

INTRODUCTION

Acrodermatitis enteropathica (AE) is a rare, autosomal recessive disorder of zinc metabolism, which usually presents in infancy, at the time of weaning, with the triad of alopecia, diarrhea and dermatitis. The cutaneous lesions are periorificial and acral in distribution. Other features include conjuntivitis, photophobia, nail dystrophy, hair shaft abnormalities, short stature, stomatitis or cheilitis, and emotional disturbances.[1]

In 1943, in Germany, professor Niels Danbolt described the condition in collaboration with the biochemist Karl Closs, and named akrodermatitis enteropathica.[2]

In Chicago (1952), a child was treated with a variety of intestinal disinfectants. It was found that diiodohydroxyquim (Diodoquin) had a surprisingly favourable effect on the skin lesions, after a few weeks of treatment.[3] But, the long-term therapy with quinoline preparations was not recommended because it could lead to retinopathy with optic atrophy in few patients.

Barnes and Moynahan, in 1973, described the association of clinical findings with low plasma zinc levels and demonstrated marked improvement with oral zinc intake.[4] Nowadays, the zinc treatment for AE has been employed around the world and assumed that must be continued indefinitely. Fortunately, nothing has emerged to suggest that long-term zinc treatment leads to any complication.[5]

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In 2001, Kun Wang et al.[6] reported the AE gene on chromosomal region 8p24.3. Next year the referred authors identified a gene SLC39A4, located in the candidate region. The gene encodes a histidine-rich protein, that was referred as "hZIP4" which is a member of a large family of transmembrane proteins, some of which are known to serve as zinc-uptake proteins. SLC39A4 is abundantly expressed in the apical membrane of mouse enterocytes, suggesting that hZIP4 transporter is responsible for intestinal absorption of zinc.[7]

In the same year, Kury et al.[8] postulated that SLC39A4 is centrally involved in AE, after studying Tunisian patients. In 2004, Kury et al. also described, in details, the molecular bases of AE.[9]

Despite all the progress of the studies, suggesting an intestinal zinc absorption deficiency in AE, the basic defect remains unknown.

In Brazilian patients we found only four reports: Guimarães and Viana (1959),[10] Campos et al. (1969),[11] Perafán-Riveros et al. (2002)[12] and Azevedo et al. (2008).[13]

CASE REPORT

A full-term Caucasian Brazilian boy, birth weight of 3130g, received breast milk at the hospital for 1 week, when he was adopted. Bovine formula feeding was started. After 18 days, periorificial and acral skin lesions appeared after watery diarrhea, weight loss and dehydratation. The diagnosis of AE was made and zinc was started, with improvement. The family moved to another city, where he received low doses of oral zinc sulfate without complete improvement. The treatment was interrupted several times, appearing cheilitis and skin lesions.

At age 2, in the first visit, no episodes of diarrhea were referred. The child was irritable, presented erythematous, scaly plaques with crusts and ulcerations on the perioral and periorbital regions, diaper area and extremities; universal alopecia; paronychia (Figure 1-A).

Laboratory studies revealed normal urinalysis and hematologic values, no parasites in the stools, low plasma levels of zinc and alkaline phosphatase.

The diagnosis of AE was reinforced. The child received adequate doses of oral zinc sulfate. After 1 month there was complete resolution of the skin lesions and start of hair growth (Figure 1-B). He gained weight and height.

In the 5-years of follow-up the boy presented only 2 episodes of Giardia lamblia infection (properly treated) and the necessity of adjustment of the oral zinc sulfate doses. Even with slight low levels of zinc he did not present skin lesions. Currently, he is very well (Figure 1-C).

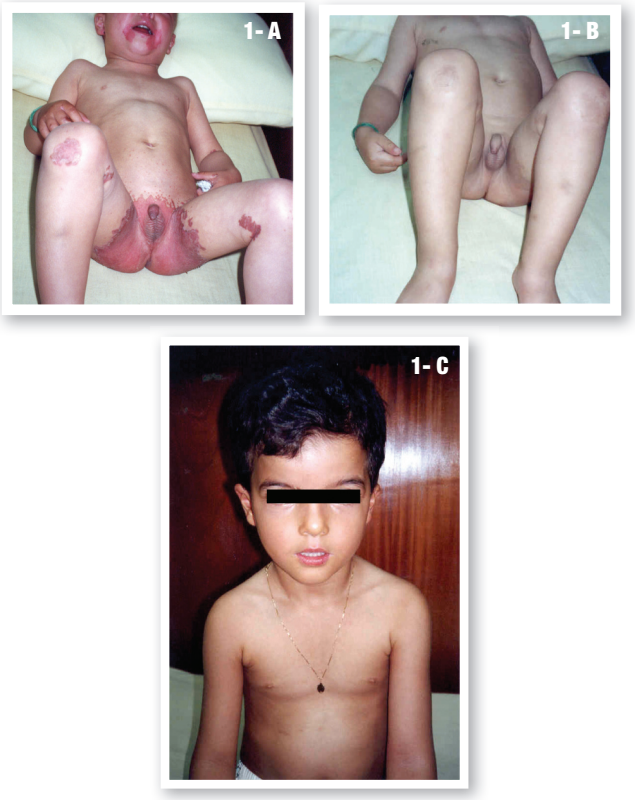

Figure 1- Acrodermatitis enteropathica. A. Acral, periorificial and diaper erythematous lesions associated with alopecia. B. Complete healing of the lesions after 1 month of zinc treatment. C. Current appearance of the patient without skin lesions and normal hair.

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DISCUSSION

AE is considered a rare autossomal recessive disease which incidence is unknown. About 30% of patients have an affected sibling.[14] As our patient was adopted we can not know about his family. AE is described in patients from several countries, with distinct mutations.[9,14] In Brazil there are few reports.[10-13]

The patient presented the characteristic triad of AE (figure 1-A) without intercurrent secondary infections.[12]

Zinc deficiencies can be divided into two groups: congenital form, called AE; and acquired forms, consequent to several basic disorders, drugs, total parenteral nutrition or prematurity.[16] Rare causes of an AE-like eruption are parenteral nutrition without zinc supplementation, Crohn´s disease, intestinal bypass procedures, gastrectomy, AIDS, anorexia nervosa and cystic fibrosis. Current studies support the hypothesis, for the hereditary form, of impaired zinc absorption from the gastrointestinal tract, caused by a genetic defect in the production, structure or function of a low molecular weight zinc-binding ligand secreted by the pancreas, present in human breast milk and not in bovine milk. It binds to zinc in the intestinal lumen and transports it into the mucosa.[16]

The disorder usually manifest at the time of weaning - or earlier, in infants who are not breast fed - and can be fatal if untreated.[6] Because the presented patient did not receive breast milk, the deficiency appeared early in life, when bovine formula feeding was introduced.[14]

Zinc is an essential mineral for humans, present in at least 100 metalloenzymes (including alkaline phosphatase), with important role in protein, carbohydrate and vitamin A metabolism; in growth, development, cell proliferation, healing and tissue repair.[17] The major concentration are localized in the kidneys, bones, muscles, eyes, esperma, skin, hair and nails. Zinc is found in red meat, bovine liver, turkey meat, sea food, crab meat, curd cheese, wheath germen, peanuts, nuts, pumpkin seeds and potable water. The greatest fountain is oister. Phytates, found in several vegetables, can difficult zinc absorption as deficiency of iron absorption. Alcool, stress or excessive comsumption of zinc (> 150mg/day) can cause nausea, fever, excessive sweat and problems in motor coordination.[12] The daily dose varies with age, the main absorption is in the duodenum and proximal small intestine with major excretion by the intestine and minor by sweat.[18] The man needs, in media, 10mg/day.

The most serious complications in AE are associated to immunodeficiency, resulting in morbidity or mortality secondary to infections. The pointed immune parameters are thymic atrophy, lymphopenia, decreased mitogen responses, decreased cell mediated immune response, decreased levels of immunoglobulin, increased recurrent infections (pneumonia, sepsis, Candida, influenza, colds).[19] Conversely, short periods of zinc supplementation substantially improve immune defense in individuals with zinc deficiency.[19]

Histopatologic examination of the skin in non specific. The skin histological changes vary with the age of the lesion. Secondary infection may complicate the picture.[20] Electron microscopy show lipid droplets and multiple cytoplasmic vacuoles in keratinocytes in the upper dermis. Desmosomes may be diminished, associated often with widening of the intercellular space.[20,21]

Jejunal biopsies are not routinely requested. No consistent abnormality of the jejunal mucosa is seen in light microscopy. Electron microscopy, however, reveals abnormal inclusion bodies in the Paneth cells. In view of the high zinc content of these cells and the response of this disease to zinc therapy, it has been postulate that a Paneth cell abnormality is concerned in its aetiology.[22]

Zinc supplementation is effective in the treatment of the disease, presumably because the increase in luminal zinc concentration is such that the diffusional component of zinc transport is stimulated.[23] Jamal et al[24] reported that zinc treatment for two patients with AE resulted in remission within the first month of therapy. That's what happened with our patient (figure 1-B). However, any short-term interruption (7-10 days) resulted in almost immediate relapse, with the reappearance of the skin lesions.[24]

There is an inverse relation between zinc and cupper that can be detected in the scalp hair of the patients. It is useful to monitor the intake of cooper in patients taken relatively high doses of zinc over a long period.[24]

To monitor the oral doses of zinc we can determine zinc levels in hair and erythrocytes, but the plasma level is the most widely used parameter for this control. Another frequent laboratory finding can be the level of urinary zinc excretion.[24] Low levels of serum alkaline phosphatase, a zinc-dependent metalloenzyme, could be a valuable indicator of zinc deficiency.[16, 25] In the patient the levels of this enzyme were low at diagnosis and normal after treatment.

Maverakis et al.[26] report that zinc replacement therapy should be startet at 3mg/kg/day of elemental zinc (there is 50mg of elemental zinc per 220mg zinc sulfate). Serum zinc levels should be monitored and the dose of zinc sulfate should be adjusted appropriately. Patients may require a higher dose thah 3mg/kg/day of zinc sulfate to normalize their genetic defect of zinc metabolism. In deficiency dermatitis caused by low dietary zinc, replacement therapy should be initiated at 1mg/kg/day of elemental zinc.

Very little information is available on the long-term prognosis of AE.[27] Some patients cease to take zinc supplements at adolescence, but in such cases chronic zinc deficiency may go unrecognized, with none or mild dermatological manifestation. In adults, chronic zinc deficiency may contribute to central nervous system disturbances such as cerebellar disturbances, parkinsonism and cortical atrophy.[28]

In conclusion, we recommend long-life careful clinical supervision for the patients with AE.

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