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Case Report

A Methylmalonic Acidemia Case Presenting with Acrodermatitis Enteropathica

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Abstract

We encountered a patient with methylmalonic aciduria associated with skin lesions resembling acrodermatitis enteropathica. This child was being fed with a low-protein diet when the skin disorder developed. A deficiency in plasma levels isoleucine, was confirmed. Supplementation of a high-caloric, protein-rich diet led to a prompt improvement of skin lesions. We assume that in our patient the skin lesions were the result of malnutrition, rather than being primarily associated with the underlying metabolic disease. To our knowledge, few reports are so far available concerning methylmalonic aciduria complicated by skin eruptions.

Keywords: Acrodermatitis Enteropathica, Children, Methylmalonic acidemia.

Introduction

Methylmalonic acidemia (MMA) is a rare autosomal recessive disease in which there is a deficiency in conversion of methylmalonic CoA to succinyl CoA. Vitamin B12 is needed to convert the methylmalonyl CoA to succinyl CoA. Some inherited conditions or B12 severe deficiency can lead to this disease (1). The principle way of methylmalonyl-coA production includes the metabolism of isoleusin, valine, threonine and methionine; so any deficiency of these amino acids can also cause MMA (2). The incidence rate of MMA is 1 in 50,000 to 80,000 newborns (3), but it is more common in countries with high amount of consanguinity and countries with no systematic newborn screening, like developing countries (4). Its typical presentations in children's first year of life are neurological symptoms like seizure, encephalopathy, and stroke. Lethargy, weak muscle tone, developmental delay, hepatomegaly, and poor eyesight are other MMA demonstrations. Inability to eat and mental disorders are patient's complains in long-term (5-7). MMA may cause coma and then death in some cases, if it remains untreated (8).

Metabolic syndromes like MMA are screened by MS/MS[1] test; but definitive diagnosis of MMA is performed by urine organic acid test (9).

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Received date: Jan 15, 2014
Accepted date: Apr 2, 2014

[1]Mass Spectrometry

Treatment consists of low protein and high calorie diet, specified medications, antibiotics and sometimes organ transplantation (10). In rare cases, the MMA patients present with acrodermatitis enteropathica presentations (11).

Acrodermatitis enteropathica is an autosomal recessive disease, which is characterized by zinc malabsorption due to a mutation of the ligand protein for zinc (12-14). Acrodermatitis acidemica is a term for skin eruption that is similar to acrodermatitis enteropathica, that is also observed in some inborn errors of metabolism such as methylmalonic academia, propionic acidemia, and maple syrup urine disease, Glutaric aciduria type I, ornithine transcarbamylase deficiency and citrullinemia (15,16).

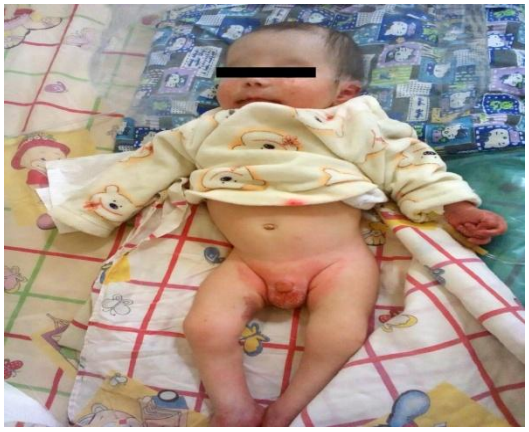
This disease causes diarrhea, alopecia, and skin inflammation in extremities (digits) and around cavities (anus, mouth, etc), due to malabsorption of zinc (17). In this study a three-month old infant boy who suffered from MMA with skin eruptions typical for acrodermatitis enteropathica is reported.

Case Report

In this study, we report a three-month old infant boy, who referred to pediatrics department of Qaem Hospital in Mashhad-Iran, due to skin lesions and lethargy. His parents were cousins. The patient has had polydactyly in upper limbs, frequent periods of respiratory distress from birth (like 3 previous children in his family, bilateral conjunctivitis and seizure.

Due to the death of three previous children in his family (at the ages of 9 days, 5 days and two years old) with presumptive diagnosis of metabolic disorders, tandem mass spectrometry was performed for him when he was 3 days old. The results of the screening showed elevated levels of propionylcarnitine (7.09 µmol/L) and significantly elevation in propionylcarnitine/ acetylcarnitine ratio (0.65) which were associated with three differential diagnosis : propionic acidemia (Propionyl CoA carboxylase deficiency), Methylmalonic acidemia (methylmalonyl-CoA mutase deficiency) and cobalamin deficiency . So the urine organic acids test was requested and the results showed an elevation in LACTIC ACID (2955 mmol/mol creatinine) and Methylmalonic acid (2870 mmol/mol creatinine) and a slightly elevated Methylcitric Acid (46.1 mmol/mol creatinine). So diagnosis of methylmalonic acidemia was confirmed at 25 days of age and the diet with MMA formula and small amount of breast milk along with related medication was recommended. We could not performing genetic tests and adenosylcobalamin test for determining subtype of MMA but because of normal level of serum hemocysteine normal level of serum glycine and ammonia and acceptable clinical response and development after medications with no need to hospitalization, our case probably is mutase or adenosylcobalamin deficient.

However, a week before hospitalization, at the age of three months anemia (Hb 6.9, Hct: 22.4 MCV: 84.2, MCH: 25.9), symmetrical vesiculobullous eczematous, dry, scaly skin lesions of the mouth, diaper and also desquamation of the palms and soles was observed (Fig.1).



Figu1: A patient with methylmalonic aciduria associated with skin lesions resembling acrodermatitis enteropathica.

Clotrimazole had no effects and these symptoms were exacerbated. Skin biopsy was not permitted but after consultation with a dermatologist, acrodermatitis enteropathica - like lesions was confirmed by clinical signs. Because of normal level of serum zinc and low level of isoleucine, deficiency of isoleucine in his powder milk and diet consumed the cause of these lesions.

Discussion

A rash similar to that of acrodermatitis enteropathica has also been reported in infants fed breast milk that is low in zinc and in those with maple syrup urine disease(MSUD), organic aciduria, methylmalonic acidemia, biotinidase deficiency, essential fatty acid deficiency, severe protein malnutrition (kwashiorkor), and cystic fibrosis(18).

Acrodermatitis enteropathica was first described by Brandt (19) in 1936 and, was named by Danbolt in 1951 with Characteristic eczematous,bullous cutaneous lesions on periorificial and acral sites and all of these clinical features are caused by zinc deficiency (20). Diagnosis of acrodermatitis enteropathica is made primarily by clinical manifestations and a low serum zinc level is confirmative. However, if the serum zinc level is normal, with characteristic clinical features and a rapid response to zinc supplementation, the diagnosis can be established (21). Many metabolic disorders, such as MMA, propionic acidemia, MSUD, Glutaric aciduria type 1, Ornitine transcarbamylase deficiency, and citrullinemia, may present with acroder-matitis enteropathica. Normal plasma zinc level is the common feature of this group of disorders; therefore, another mechanism might have a role in the appearance of cutaneous lesions in acrodermatitis enteropathica. This mechanism is most likely related to amino acid deficiency(15). In a report by Koch et al, two MSUD cases were described with eruptive dermatitis that resolved after supplementation of the deficient amino acid, in particular isoleucine (22). Methylmalonic acidemia and propionic acidemia are occasionally reported to present with cutaneous manifestations; A low-protein diet with supplementation of essential amino acids is the therapy of choice for organic acidemias, but if the diet is strictly limited in branched-chain amino acids, the most critical one being isoleucine, cutaneous lesions resembling acrodermatitis enteropathica may result (23) Similar cutaneous lesions have been reported with urea cycle defect which include citrullinemia, ornitine transe carbamylase deficiency, and carbamoyl phosphate synthetase deficiency. In all of these cutaneous lesions, arginine accumulation is the main cause of the typical clinical manifestations. Arginine restriction in the diet is the mainstay of treatment, although excessive restriction leads to acrodermatitis enteropathica. In a case with citrullinemia similar rash reported in attribution to arginine deficiency (24).

According to these reports and our case excess or deficient essential amino acids causes acrodermatitis entropathica.

Conclusion

This finding indicates that serum zinc level is not an absolute value in diagnosis of acrodermatitis enteropathica. Also aminoacidopathies in inborn errors of metabolism plays the major roll in physiopathology of this kind of skin eruption especially in methylmalonic acidemia so replacement of related deficient amino acid will effectively cure the rash.

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