An Unusual Case of Biotinidase Deficiency with Fingertip Desquamation

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Abstract

Biotinidase deficiency (BD) is an autosomal recessively inherited inborn error of metabolism that causes multisystemic manifestations, including developmental delay, seizures, hypotonia, vision problems, hearing loss, ketolactic acidosis, and various cutaneous findings at the early stages of life. Treatment consists of oral biotin that is effective in the prevention of complications. We present a case of a 4-year-old boy with partial BD with fingertip desquamation that could be resolved by increasing biotin dosage.

Keywords: Biotin, biotinidase deficiency, desquamation

Introduction

Biotin is a water-soluble vitamin that is the coenzyme of several enzymes that play an essential role in carboxylation reactions. Biotinidase is responsible for the cleavage of biotin from biocytin and dietary sources. Biotinidase deficiency (BD) is an autosomal recessively inherited inborn error of metabolism (IEM) that causes multisystemic manifestations, including cutaneous findings.[1,2]

We present a case of a 4-year-old boy with partial BD deficiency with fingertip desquamation that could be resolved by high-dose oral biotin.

Case Report

A 4-year-old boy with known partial BD (biotinidase level: 1, normal level >4.2 nmol/ml/s) was admitted due to fingertip desquamation [Figure 1]. He was the first child of consanguineous parents (first-degree cousins). BD was diagnosed in the neonatal period by neonatal birth screening (NBS), and oral biotin 10 mg/day was initiated. He had no history of fever or infection, hair loss, or seizures. He denied contact with any chemicals or irritants. Desquamation was only limited to the fingertips of hand, not involving the palms and soles. Initial diagnosis of the desquamation was attributed to eczema, and discontinuation using liquid soap was suggested. Moreover, topical steroid was administered for 10 days. He was referred to the metabolism department for further evaluation, since the desquamation persisted despite treatment. Upon admission, he was in good condition. His height and weight were within normal centiles. He did not have any other cutaneous finding apart from desquamation of fingertips. Laboratory analyses revealed normal complete blood count, antistreptolysin O antibody titer, ferritin, plasma zinc level, and vitamins A and E. Incompliance to biotin treatment was denied by parents.

Genetic analysis of BTD gene performed in our center revealed a compound heterozygous mutation (c.98–104del7ins3 and c.1330G>C, p.D444H).

Since the finger desquamation persisted, biotin dosage was increased to 20 mg/day. Interestingly, the desquamations reappeared when the patient could not get biotin for a couple of days since he was out of supply, also involving

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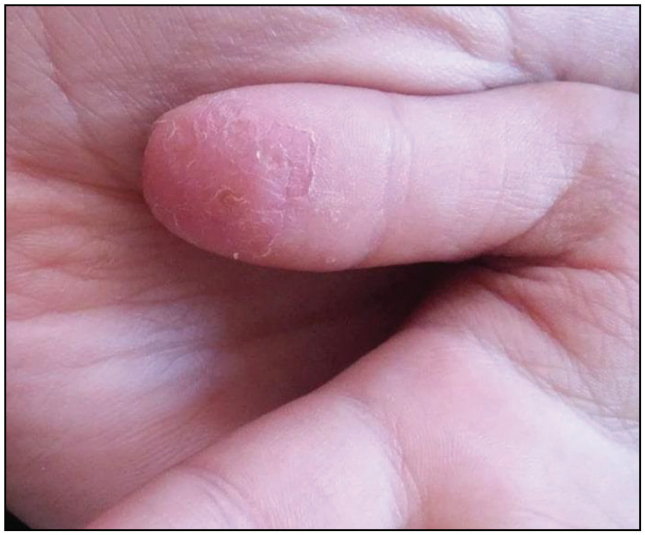

Figure 1: Fingertip desquamation of the presented case

the palms [Figure 2], and again resolved after restarting of therapy.

Discussion

BD is an autosomal recessively inherited disorder with variable symptoms, especially with neurological and dermatological involvement.[1] Biotin is a cofactor of many carboxylases including pyruvate carboxylase, propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase. Due to the deficient activity of these enzymes, the processing of proteins, fats, and carbohydrates is altered in BD that affects the energy metabolism and leads to multisystemic symptoms.[2]

The incidence is suggested to be 1 in 60,000 and may be higher in countries where consanguineous marriages are prevalent, as in Turkey.[2] In many countries, patients are diagnosed at the newborn period by NBS.[3]

The responsible gene for the disease is BTD that is located on chromosome 3p25. Three hundred and sixty-four different variants have been reported up-to-date. Genotype–phenotype correlation is difficult due to the variability of symptoms.[4]

BD is categorized as profound or partial, according to the residual enzyme activity (<10% in profound deficiency, between 10% and 30% in partial deficiency). Although patients with profound BD usually have a mild clinic, severe symptoms have been reported if untreated.[5] Profound BTD deficiency occurs due to the homozygous or compound heterozygous mutations.[4] The underlying mutations are the determinants of the enzyme activity and thus the severity of symptoms.[2] Canda *et al*.[6] have reported the largest cohort of BD from Turkey in 2012, where p.D444H, p.R157H, and c.98_104delinsTCC were the most commonly detected variants. Our patient is found to be compound heterozygous for the two most commonly reported mutations in Turkey.

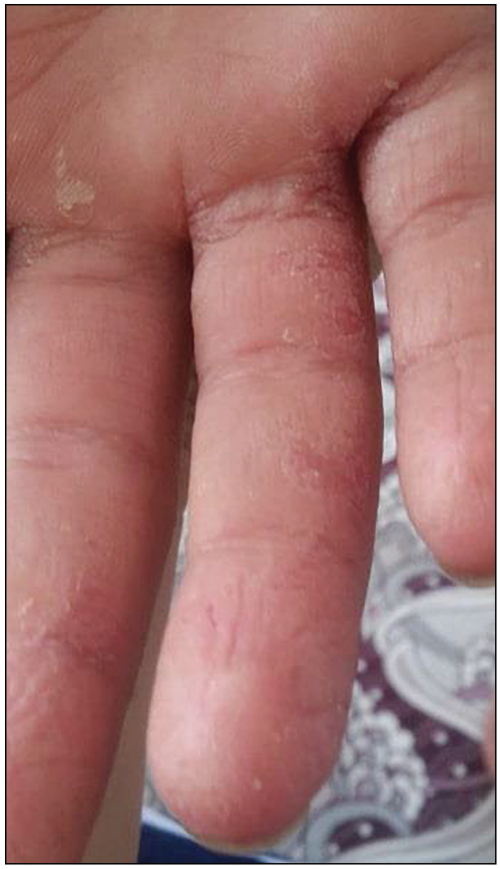

Figure 2: Finger desquamation during noncompliance to treatment

Cutaneous signs related to BD include rash, eczema, alopecia, scaly erythematous plaques over the flexors and perioral areas, and seborrheic dermatitis-like eruptions.[7] Lichenification, crusting, and secondary *Candida* infections may be seen in severe cases. Thin hair, total or partial alopecia have also been reported.[8] The skin changes of BD are suggested to be related to abnormalities in lipid metabolism, since the accumulating propionyl-CoA metabolites due to PCC deficiency may cause an increase in odd-chain fatty acids. Supplementation of biotinidase-deficient mice with omega-6-polyunsaturated fatty acid has been shown to prevent dermatological manifestations of BD.[2]

Diagnosis is usually made by the determination of biotinidase activity in plasma or serum by colorimetric assay method.[2] The exact diagnosis is made by the molecular genetic analysis of BTD.[1-3]

Standard treatment of profound BD is 10–20 mg/day oral biotin therapy that is usually sufficient for the prevention of irreversible neurological symptoms including optic atrophy, hearing loss, or cognitive disability.[5] Treatment may improve or resolve mild symptoms that may reoccur due to noncompliance with biotin treatment.

Many metabolic disorders present with cutaneous findings.[9] Well-known IEMs that lead to skin findings are summarized in Table 1. Periorificial desquamation involving moist areas is most commonly defined in IEMs involving pathways

Table 1: Inborn errors of metabolism that cause skin eruptions

Disease name	Type of skin lesion	Additional clinical findings
Biotinidase deficiency	Desquamative, periorificial eruptions	Massive ketosis and acidosis, stridor, convulsions, hypotonicity, mental retardation, optic atrophy, and sensorineural deafness
Holocarboxylase synthetase deficiency	Desquamative, periorificial eruptions	Similar to biotinidase deficiency, more severe
3-MCC deficiency	Similar to biotin deficiency	
Methylmalonic aciduria/ propionic aciduria	Desquamative, periorificial eruptions, psoriasiform lesions, and alopecia (skin lesions are mainly due to natural protein restriction)	
Mevalonic aciduria/hyper-IgD syndrome	Morbilliform rashes and erythematous macules	Dysmorphic features, global developmental delay, cataract, arthralgias with periarticular edema, recurrent febrile crises with lymphadenopathy, hepatosplenomegaly, vomiting, and diarrhea
Homocystinuria	Skin ulceration due to thromboembolic disease	
Acrodermatitis enteropathica	Bullous, pustular dermatitis on extremities and periorificial areas	Diarrhea and zinc deficiency
Sulfite oxidase deficiency	Eczema	
Prolidase deficiency	Lower extremity ulcers	Mental retardation, ophthalmoplegia, splenomegaly, dysmorphic features, and susceptibility to infections. Severe immunological abnormalities
Lysinuric protein intolerance	Lupus-like lesions	Hyperammonemia, failure to thrive, severe renal involvement, and pulmonary involvement
Tyrosinemia type II	Hyperkeratotic lesions of palms and soles	Corneal ulcers

3-MCC: 3-Methylcrotonyl-CoA carboxylase

related to biotin metabolism.[7] Any relationship between fingertip desquamation and BD has not previously been reported in the literature, and reports of atypical cases are limited. For example, Navarro *et al*. have reported an infant with erythematous scaling in the lumbosacral region.

Fingertip desquamation is a frequently encountered condition in childhood that is usually benign. Various diseases may cause desquamation of fingertips including eczema, exfoliative keratolysis, allergic contact dermatitis, and psoriasis. Periungual desquamation is also a hallmark of Kawasaki disease. Congenital syphilis and bacterial toxin-mediated disorders are also known to cause desquamation of hands and feet.[10]

In the presented case, although scaling of the fingertips may not be directly related to BD, the refractive nature of the lesions may be due to the disease since topical treatment did not have any effect. Furthermore, they may be an atypical presentation of BD. Nevertheless, increasing the dosage of biotin has resolved the lesions.

Conclusion

Cutaneous findings of a patient with known metabolic disorder may suggest inadequate treatment or poor metabolic control.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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