

## Biotinidase Enzyme Deficiency ( Case Report )

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### Abstract

Biotin deficiency is very rare in the world .We had reported a case of biotin deficiency "for the first time in our country" in a family from Wasit Province / Hay District. This family includes seven children, unfortunately three of them died before the diagnosis of this disease, they are presented with ataxia, hypotonia, developmental delay, conjunctivitis, skin rash, dermatitis , alopecia, hearing difficulty , breathing problems and recurrent chest infections.

The disease was proved after therapeutic trial with vitamin replacement and through biotinidase enzyme assay "which is the most effective enzyme by which the body's cells can using the biotin effectively". This test was done by sending blood samples to one of the medical laboratories in France. Now the children were doing very well on lifelong treatment with activated biotin .

### المستخلص

نقص البايوتين جدا نادر في العالم . لقد وثقنا حاله لمرض نقص فيتامين البايوتين "وذلك لأول مره في العراق " لدى عائله في محافظة واسط / قضاء الحي . تضم هذه العائله سبعة اطفال ولسوء الحظ فقدت ثلاثة منهم قبل تشخيص هذا المرض. هؤلاء الاطفال كانوا يعانون من وهن عضلي شديد وتاخر في النمو والتهاب ملتحمه العين مع تقرحات جلديه شديده وتساقط الشعر وصعوبه في التنفس مع التهابات رئويه متكرره مع عدم توازن عند المشي . لقد تم التحقق من المرض بواسطة محاولة علاجه بالبايوتين مع ارسال عينات من دم الاطفال الى احد المختبرات الفرنسيه للتحري عن نقص انزيم "البايوتيديز" ذلك الانزيم المسؤول عن تنشيط فيتامين البايوتين في الجسم كي يؤدي عمله بشكل صحيح وفعال.

الان وبفضل الله تعالى الاطفال بصحه طيبه تحت العلاج المستمر بفيتامين البايوتين الفعال.

### Introduction

Biotin (Vitamin H) also called (vitamin B-7) which is a member of the B-vitamin family and good sources are found in egg yolk, kidney, milk, soya, barley, Brewer's yeast and royal jelly (1).

Biotin is a coenzyme in the metabolism of fatty acids and leucine, and it plays a role in gluconeogenesis. Biotin is necessary for cell growth, the production of fatty acids, and the metabolism of fats and amino acids. It plays a role in the citric acid cycle, which is the process by which biochemical energy is generated during aerobic respiration. Biotin does not only assists in various metabolic reactions but also help to transfer carbon dioxide. Biotin may also be helpful in maintaining a steady blood sugar level. biotin is a cofactor responsible for carbon dioxide transfer in several carboxylase enzymes ( 1,2,3 ).

Biotin deficiency is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH). This means that Biotin deficiency, or a subtype of Biotin deficiency, affects less than 200,000 people in the US population ( 4,5,6).

Symptoms of overt biotin deficiency include:

- Hair loss (alopecia)
- Conjunctivitis
- Dermatitis in the form of a scaly red rash around the eyes, nose, mouth, and genital area.
- Neurological symptoms in adults such as depression, lethargy, hallucination, and numbness and tingling of the extremities.
- If untreated the patient will develop metabolic acidosis, coma and death ( 1,7,8 ).

Inherited metabolic disorders characterized by deficient activities of biotin-dependent carboxylases are termed multiple carboxylase deficiency. These include deficiencies in the enzymes holocarboxylase synthetase or biotinidase. Holocarboxylase synthetase deficiency prevents the body's cells from using biotin effectively, and thus interferes with multiple carboxylase reactions ( 9,10 ).

Biotinidase deficiency is not due to inadequate biotin, but rather to a deficiency in the enzymes that process it. Biotinidase catalyzes the cleavage of biotin from biocytin and biotinyl-peptides (the proteolytic degradation products of each holocarboxylase) and thereby recycles biotin. It is also important in freeing biotin from dietary protein-bound biotin ( 11,12 ).

The absence of biotinidase results in biotin deficiency. symptoms may appear later, when the child is several months or several years old; symptoms may develop as early as 1 wk of age. Therefore, the term "late form" does not apply to all cases and can be misleading. The delay is presumably because of the presence of sufficient free biotin derived from the mother or the diet. Atopic or seborrheic dermatitis, alopecia, ataxia, myoclonic seizures, hypotonia, developmental delay, sensorineural hearing loss, and immunodeficiency (from T-cell abnormalities) may occur. Asymptomatic children and adults with this enzyme deficiency have been identified in screening programs. Most of these individuals have shown to have partial deficiency of the enzyme activity ( 1,13 ).

**Laboratory Findings** :-diagnosis can be established by measuring enzyme activity in the serum. Individuals with profound biotinidase deficiency have less than 10% of mean normal serum biotinidase enzyme activity. Individuals with partial biotinidase deficiency have 10%-30% of mean normal serum biotinidase enzyme activity. A simplified method for mass screening of newborn infants is now available and is in use in the United States and around the world ( 1,12,13 ).

**Treatment** :- All symptomatic children with profound biotinidase deficiency improve when treated with 5-10 mg of oral biotin per day results in a dramatic clinical and

biochemical response.. All individuals with profound biotinidase deficiency, even those who have some residual enzymatic activity, should have lifelong treatment with biotin. Children with vision problems may benefit from vision aids; those with hearing loss will usually benefit from hearing aids or cochlear implants, and those with developmental deficits from appropriate interventions ( 1,13 ).

**Prevention:-**prevention of primary manifestation in children with biotinidase deficiency identified by [newborn screening](#) should remain asymptomatic if biotin therapy is instituted early and they are continuously maintained on therapy ( 13,14 ).

### Case Report

We present a very rare case of biotinidase enzyme deficiency (for the first time in our country) in a family live in a village in AL- Hay District / Wasit Province.

This family consists of seven children with their parents , three of these children died from the same illness before the diagnosis was established.

The parents are relatives ( second degree relatives ) and they are healthy  
The alive siblings are:-

\*10 yrs. Female

\* 8 yrs. Female

\* 4 yrs. Male

\*3 yrs. Male

Those four children are presented with ataxia, hypotonia, developmental delay, conjunctivitis, skin rash, dermatitis , alopecia, seizures, hearing difficulty , breathing problems and recurrent chest infections.

The family consulted many well- known doctors in major centers in our country and they were diagnosed on clinical base as a fatal( un treatable) disease called ( **Kinky Menke syndrome** ) , under this heading the family lost three of it's children.

They consulted many humaterian organizations to be treated outside the country, but their diagnosis by this untreatable disease prevents that.By chance, the father with his children consulted me seeking any help, bringing all the medical reports they collected them within more than ten years. From the general looks of these children, and by" the help of my god" it comes to my mind that those children suffer from some sort of vitamin deficiency according to their signs and symptoms.

We try therapeutic trial with two different preparations of vit.B.complex . We notice the one that contains biotin in it's composition gives dramatic response and all the signs and the symptoms of the disease disappeared within one month on treatment. But biotin deficiency rarely, if ever, occurs in healthy individuals who consume a regular diet unless they are being treated either with certain anticonvulsants or with broad-spectrum antibiotics. The extremely low prevalence of biotin deficiency is probably the result of a combination of factors. First, the daily requirement for biotin is low (approximately 150-300 µg/d). Second, almost all foods contain significant quantities of biotin, and many widely consumed foods are relatively rich in biotin. Third, the intestinal flora synthesizes

significant quantities of biotin, and at least a portion of that biotin is believed to be absorbed into the bloodstream. Fourth, a significant fraction of the body's biotin is recycled; that is, a given molecule of biotin may be repeatedly used before it is eventually lost from the body in the feces or urine.

For these reasons, we must look for a hereditary disease causing this severe type of deficiency to the degree that affects all the family members and after reading more about this subject, we found that dietary biotin is bound to proteins; free biotin is generated in the intestine by the action of digestive enzymes, by intestinal bacteria, and perhaps by biotinidase. The latter enzyme, which is found in serum and most tissues in the body, is also essential for the recycling of biotin in the body by releasing it from the apoenzymes (carboxylases). Deficiencies in biotinidase result in malfunction of all the carboxylases and in organic acidemia.



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**DOSAGE DE L' ACTIVITE BIOTINIDASE PLASMATIQUE**  
 Méthode colorimétrique quantitative

Activité exprimée en nmol/min/ml de sang total  
 Prélèvements sur Papier Guthrie

Khalil Tahir (1960 Père)	1,9
Djamila (1960 Mère)	1,7
Ibtihal (1982 Fille ainée)	0,3
Raghad (1989 Fille)	0,3
Tahir (1994 Garçon)	0,4
Ali (1995 Garçon)	0,6

Contrôles : 4,4 à 12,0

Commentaire : Les quatre enfants Ibtihal, Raghad, Tahir et Ali ont une activité Biotinidase effondrée (< 5% d'activité résiduelle). L'activité observée pour les deux parents est de type hétérozyote.

Validation Analytique  
 J.Bardet, Technicienne

Validation Biologique  
 D.RABIER, MCU-PH

Secteur exécutant : Acides Aminés, Acides Organiques : responsable D. RABIER

Deficiency of biotinidase enzyme can be inherited as an autosomal recessive and by the help of one of the French humaterian organizations we sent blood samples from parents and their children for biotinidase enzyme assay for one of the medical laboratories in the France capital "Paris" and the result revealed very low enzymatic activity in whole children and both parents are carrier for the disease. Now, they are doing well on oral free biotin , all signs and symptoms are disappeared and they are thriving very well.

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