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Case Report

Biotinidase Deficiency: Early Presentation

Somya Chaturvedi, Jayashree Nadkarni*, Rashmi Randa, Shweta Sharma, Rajesh Tikkas
Department of Paediatrics, Gandhi Medical College and Associated Kamla Nehru and Hamidia Hospital, Bhopal (M.P.) India

***Corresponding author**
Dr. Jayashree Nadkarni
Email: jayadn2007@gmail.com

Abstract: A 2 month old male child presented with fever, seizures, metabolic acidosis, alopecia and dermatitis. Diagnosed to be case of biotinidase enzyme deficiency. Identification of this disorder is important as it is easily treatable and the patients show dramatic response to therapy. It can prove fatal if not diagnosed.
Keywords: alopecia, dermatitis, biotinidase enzyme deficiency.

INTRODUCTION

Biotinidase recycles the vitamin biotin. Biotinidase deficiency is a rare metabolic disorder with autosomal recessive inheritance which can cause dermatological manifestations and lead to severe neurological sequelae if untreated. The symptoms can be successfully treated or prevented by administering pharmacological doses of biotin. Holocarboxylase synthetase deficiency also has similar manifestations and needs to be differentiated.

It was first described by Wolf and colleagues in 1983[1]. Biotin, a vitamin B complex is necessary to activate the carboxylase enzymes system which is essential for the metabolism of amino acids, carbohydrate, and fatty acids. Biotin is normally required in a very small quantity as most of it is recycled by biotinidase enzyme. With biotinidase deficiency there is depletion of body biotin stores which leads to severe metabolic consequences. Clinical manifestations include neurological, dermatological, immunological, and ophthalmological abnormalities. We report a case of profound biotinidase deficiency that was being treated for chronic skin manifestation and diagnosis was made when his condition deteriorated. Biotinidase deficiency, can be profound (<10% enzyme level) or partial (10-30% enzyme level).

CASE REPORT

A 2-month old boy, born of nonconsanguineous marriage, presented with fever and abnormal movements (tonic associated with up rolling of eyeballs, multiple episodes) Baby was hospitalized with status epilepticus and impending respiratory failure and needed ventilation. He was diagnosed as having meningitis after CSF examination.

On examination, patient was found to have loss of eyelashes, excessive hair fall, and multiple episodes of myoclonic jerks, dermatitis and conjunctivitis which the mother had noticed since around 1 month of life. He was treated symptomatically, followed by anticonvulsant therapy with phenytoin. Convulsions improved and after two days he was removed from ventilator and put on intranasal oxygen. Soon after he was started gavage feeds of expressed breast milk and after a few days started taking breast feeds well.

Laboratory investigations revealed leukocytosis, normal liver functions, serum ammonia and serum electrolytes, Blood gas analysis showed increased anion gap metabolic acidosis. Baby also had persistent ketonuria, acidic urine. Blood lactate levels were significantly raised. MRI brain was normal.

He was investigated further for a metabolic disorder in view of poor therapeutic response and a history of elder sibling dying with similar complains. Plasma and urine aminoacido gram was normal. Tandem mass spectrometry (TMS) revealed increased C5 hydroxy carnitine levels, suggestive of holocarboxylase deficiency.

Specific enzyme assay showed deficient biotinidase activity of 0.2 nmol/min/mL (normal > 5 nmol/min/mL). A diagnosis of biotinidase deficiency was made and he was started on oral biotin (10 mg/day). He showed dramatic improvement within 24

hours with decrease in hyperventilation, normalization of blood gas, and improved sensorium. By the end of a week there had been considerable improvement in skin lesions and new hair growth was noticed. All anticonvulsant treatment was stopped.

Fig 1: Showing alopecia and dermatitis

DISCUSSION

Biotinidase deficiency is a rare metabolic disorder with an estimated incidence of 1:61067 populations, though severe or profound disease is much rare (1: 137401 populations) [2]. Very few reports of biotinidase deficiency could be traced in Indian literature, some of which were detected on routine neonatal screening [3-6].

Biotin is a water-soluble vitamin that serves as an essential coenzyme for five carboxylase in mammals. Biotin-dependent carboxylase catalyzes the fixation of bicarbonate in organic acids and play crucial roles in the metabolism of fatty acids, amino acids and glucose. Carboxylase activities decrease substantially in response to biotin deficiency. Biotin is also covalently attached to histones; biotinylated histones are enriched in repeat regions in the human genome and appear to play a role in transcriptional repression of genes and genome stability.

Biotin deficiency may be caused by insufficient dietary uptake of biotin, drug-vitamin interactions and, perhaps, by increased biotin catabolism during pregnancy and in smokers. Biotin deficiency can also be precipitated by decreased activities of the following proteins that play critical roles in biotin homeostasis:

1. The vitamin transporters sodium-dependent multivitamin transporter and monocarboxylate transporter 1, which mediate biotin transport in the intestine, liver and peripheral tissues, and renal reabsorption;
2. Holocarboxylase synthetase, which mediates the binding of biotin to carboxylases and histones; and
3. Biotinidase

Biotinidase (BTD), a ubiquitous mammalian cell enzyme, is present in high levels in the serum, liver, and kidneys. Its primary enzymatic function is to cleave the vitamin biotin (also known as coenzyme R, vitamin H, or vitamin B7) from the organic compound biocytin. Biotin is recycled in the body when biotinidase liberates biotin from endogenous and dietary proteins. Recycling maintains a pool of biotin to serve as a critical cofactor for gluconeogenesis, fatty acid synthesis, and branched chain amino acid catabolism [1].

Inheritance

Mendelian inheritance is autosomal recessive. Both biological parents must contribute the biotinidase gene mutation for this organic acid deficiency to occur, as two altered gene copies are required. Biotinidase deficiency heterozygous carriers can be identified via mutation assay

The gene that encodes biotinidase, called BTD, is cytogenetically located on the short arm (p) of chromosome 3, band 25 (3p25). The most common BTD mutation, 98-104del7ins3, is present in about 50% of symptomatic children. A less common BTD mutation, Arg 538 R→C, has also been described. The BTD mutation known to cause partial deficiency is p D444H [9]. Research by Wolfe cites the difficulty of correlating genotypes with phenotypes, indicating that age at onset of clinical signs and the disease path

primarily depend on the amount of functioning biotinidase present [1].

Clinical Presentation

Depends on the severity of enzymatic defect. Profound defects usually manifest between 3-6 months of age with –

a) Neurological manifestations (seizures, hypotonia, and develop-mental
b) Delay);
c) Skin manifestations (eczematous skin rash, seborrheic dermatitis, alopecia); and
d) Respiratory problems (hyperventilation, laryngeal stridor and apnea).
e) (d)Conjunctivitis is common.
f) Immunologic deficiencies-Abnormalities in cellular immunity can result from biotin deficiency. Chronic and potentially lethal fungal infections characterize immunologic dysfunction.

Our case had skin manifestations and conjunctivitis and probably his symptoms got aggravated by a secondary infection Many symptomatic children with biotinidase deficiency exhibit various neuroimaging abnormalities e.g. cerebral edema, attenuated white matter signal, cerebral atrophy, and compensatory ventricular enlargement. Neuroimaging features may improve or become normal after biotin treatment [7]. Candidiasis is common, which may be related to immunological dysfunction following accumulation of toxic metabolites or biotin deficiency itself. Children with partial biotinidase deficiency (10-30% activity) may present with milder symptoms, especially during stress e.g., infection.

Biotinidase deficiency may be detected on newborn screening [8] or by prenatal molecular diagnosis for mutations, recommended in case of previous affected child in the family. Recently, molecular genetic tests have been used for detection of carrier state [9]. Most cases with biotinidase deficiency exhibit metabolic ketolactic acidosis, mild hyperammonaemia, and organic aciduria. Apart from common neonatal conditions e.g. sepsis, meningitis or epilepsy, biotinidase deficiency may be confused with holocarboxylase deficiency previously called early-onset or infantile multiple or combined carboxylase deficiency.

A simplified newborn screening on dried blood spots is presently in use [8, 9]. Diagnosis of biotinidase deficiency is confirmed by measurement of enzyme activity in serum. There is also a need to screen asymptomatic siblings.

Fig 2: closer look of face showing dermatitis

Treatment

Therapy for biotinidase deficiency is oral biotin; typically prescribed at a starting dose of 5-10 mg/d. Treatment is with free biotin. Bound biotin, present in multivitamin supplements, does not treat the body deficiency. Biotinidase deficiency needs life-long biotin supplements upto 40mg/day. Raw eggs, containing avidin that binds biotin, must be avoided.

CONCLUSION

The prognosis is excellent though some features e.g. optic atrophy; hearing loss or developmental delay may not be reversible and should be addressed with periodic evaluations and relevant interventions [10, 11]. In this largest cohort study of symptomatic Biotinidase deficient children from India Outcome was favourable in cases where early diagnosis was made and prompt treatment was instituted [12]. So,

early and timely supplementation of biotin improves the neuro devlopmental outcome.

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