BIOTINIDASE DEFICIENCY- A TREATABLE INHERITED METABOLIC DISORDER

Bushra Afroze
Department of Pediatrics and Child Health, Aga Khan University Hospital, Pakistan

Correspondence to: Bushra Afroze, Department of Pediatrics and Child Health, Aga Khan University Hospitals, Stadium Road, P.O Box 3500, Karachi 74800, Pakistan. Tel: 92-21-34864728, Fax: 92-21-34854294, Email: bushra.afroze@aku.edu

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ABSTRACT

Biotinidase deficiency is an autosomal recessive inherited metabolic disorder, in which the enzyme biotinidase involved in the biotin cycle is defective resulting into lack of recycling of biotin. Individuals with untreated biotinidase deficiency usually manifest neurological and cutaneous abnormalities. Treatment of biotinidase deficiency is very rewarding for the physicians and satisfying for the patients and their families, as the clinical features not only respond dramatically to oral biotin therapy but can be prevented if oral biotin therapy is initiated in asymptomatic individuals. Patients with biotinidase deficiency in Pakistan are often not diagnosed or are misdiagnosed due to poor awareness of the condition amongst the health care providers of Pakistan. This leads to lack of accurate treatment resulting in significant morbidity and mortality of patients from a metabolic disorder, which is treatable. This short review is focused on the clinical manifestations, biochemical features and treatment of biotinidase deficiency, which will help in increasing awareness of biotinidase deficiency among physicians.

INTRODUCTION

Biotinidase deficiency (BD) is an autosomal recessive, inherited metabolic disorder in which the vitamin, biotin cannot be appropriately recycled. Overall global incidence of BD is 1 in 60,000 live births. However, incidence of BD varies between countries, with incidence in Brazil as high as 1 in 9,000 and possibly higher incidences in countries with high consanguinity, such as Turkey and Saudi Arabia. Incidence of BD in Pakistan is unknown. Patients with BD are often not diagnosed due to the lack of awareness among health care provider and local non-availability of the diagnostic test for BD.

Children with BD usually present with neurological symptoms like seizures, ataxia, hypotonia, developmental delay and/or skin rashes and alopecia in the first year of life. However, some patients with BD do not manifest symptoms until adolescence or adulthood. But asymptomatic BD in children and adults has also been reported.

Treatment of BD with oral biotin is simple and extremely rewarding. Therefore, currently all newborn screening programs in the United States and more than 30 other countries screen their newborns for BD.

This short review on BD focuses on the clinical and biochemical features of BD, which will enable early recognition and prompt management to prevent morbidity as well as mortality from an inherited metabolic disorder.

THE BIOTIN CYCLE AND BIOTINIDASE DEFICIENCY

Biotin is a water-soluble B-complex vitamin, which is present in small amounts in different foods. The unbound form of biotin is actively transported across the intestine into the free biotin pool. Biocytin, the protein-bound form is processed by biotinidase enzyme, after which it enters into free biotin pool. Biotin is coenzyme for four carboxylases; propionyl-CoA (PCC), methylcrotonyl-CoA (MCC), pyruvate carboxylase (PC) and acetyl-CoA carboxylase (ACC), that are involved in amino acid catabolism, fatty acid synthesis and gluconeogenesis. In the hepatocytes, enzyme holocarboxylase synthetase covalently attaches biotin to (inactive)
synthetase covalently attaches biotin to (inactive) apocarboxylases to form (active) holocarboxylases. (PCC, MCC, PC and ACC. Figure 1)

**BTD - HUMAN BIOTINIDASE GENE**

Human biotinidase gene, BTD has been cloned, sequenced and characterized. It was localized to chromosome 3p25 and consists of 4 exons with a length of 1629 base pair. So far 140 mutations in BTD gene have been identified that cause BD. No clear genotype-phenotype correlation has been shown, with different frequencies of mutations in symptomatic patients and patients diagnosed by newborn screening.

**COMMON NEUROLOGICAL FEATURES**

Seizures occur in more than 70% of symptomatic children with profound BD. Variable types of seizures and electroencephalography (EEG) findings are seen in BD. Seizures are often intractable and resistant to anticonvulsants and very sensitive to biotin. BD should be considered in any child with intractable seizures. Hyptonia, variable degree of developmental delay and ataxia are seen in untreated individuals as they grow older. Often BD patients show a progressive encephalopathy but some affected individuals may have period of acute deterioration with apparent normal intervals. BD affected individuals who present in later childhood or adolescence exhibit motor limb weakness and spastic paresis rather than the classical symptoms ascertained in younger children.

Various abnormal findings are seen in magnetic resonance imaging (MRI) of individuals with BD, which most commonly includes cerebral/cerebellar atrophy, ventriculomegaly, widened extracerebral spaces, subdural effusion, caudate involvement and basal ganglia calcification. White matter changes in periventricular area and cystic degeneration have also been reported. Necrotizing lesions as seen in Leigh’s disease are reported; however, hippocamal and para hippocamal cortex are most affected in BD.

**NEUROMUSCULAR AND SPINAL ABNORMALITIES**

Untreated individuals with BD have been described with various neuromuscular features like proximal muscle myopathy, severe loss of motor units, distal axonal polyneuropathy and decreased response to pain. Spinal cord abnormalities including abnormal signals in cervicothoracic region and diffuse abnormal signals in white matter from cervicomedullary junction to the conus have been described.

**CUTANEOUS FEATURES**

Untreated BD in children usually manifests as a maculopapular eruption typically described as scaly and erythematous rash especially in moist and periorificial areas. More severe cases may show lichenification, crusting and open lesions that may get infected by Candida. Children also usually have total or partial alopecia, which may involve eyebrows and eye lashes resulting into sparse or absent eye brows and eye lashes, as described.

**OPHTHALMOLOGICAL FEATURES**

About half of untreated BD individuals present with variable ophthalmological features, which includes optic atrophy, visual impairment, progressive epithelial dysplasia, abnormal eye movements and abnormal visual evoked potentials. Conjunctivitis, fungal infections, corneal ulceration and blepharitis are also commonly seen. In older children, loss of visual acuity and scotomata are common features instead of the usual ophthalmological features observed in younger children.

**HEARING IMPAIRMENT**

Sensorineural hearing loss is a feature seen in about 76% of individuals with untreated BD. Considerable variability is seen in the characteristics of hearing loss including: absent brain stem auditory evoked responses, absent responses at high frequencies and delayed latencies or slow conduction.

**BIOCHEMICAL CHANGES IN BLOOD, URINE AND CEREBROSPINAL FLUID**

Metabolic ketoacidosis, lactic acidosis and hyperammonemia may be seen in children with BD especially in phases of metabolic decompensation. Lactate concentration is often increased in cerebrospinal fluid (CSF). Urine organic acid analysis is most helpful biochemical tool that indicates diagnosis of BD. It shows elevated excretion of 3-hydroxyisovaleric acid, lactic acid, 3-hydroxypropionic acid and 3-methylcrotonylglycine. Similar pattern of organic aciduria can be seen in holocarboxylase synthetase deficiency, which has to be differentiated from BD. It must be recognized that urine organic acid analysis is not helpful in up to 20% of symptomatic children ultimately found to have profound BD.
Table 1: Clinical and Biochemical differentiation between biotinidase deficiency and holocarboxylase synthetase deficiency.

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Biotinidase deficiency</th>
<th>Holocarboxylase synthetase deficiency</th>
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<tbody>
<tr>
<td>Hypotonia</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lethargy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ataxia</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Seizures</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Myopathy/peripheral neuropathy</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Sensorineural hearing impairment</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Skin rashes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alopecia</td>
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Biochemical Features

| Metabolic acidosis                    | +/-                     | +                                    |
| Lactic acidosis                       | +                      | +                                    |
| Hyperammonemia                        | +                      | +                                    |
| Ketonuria                             | +                      | +                                    |
| Organic aciduria                      | +                      | +                                    |
DIAGNOSIS & DIFFERENTIAL DIAGNOSIS OF BIOTINIDASE DEFICIENCY

Diagnosis of BD is based on demonstration of deficient enzyme activity in serum or plasma using either semiquantitative fluorometric method using biotin 6-aminquinoline as substrate or semiquantitative colorimetric method using N-biotinyl-β-aminobenzoic acid as substrate. Dried blood spots on filter paper are used for this purpose. Based on serum/plasma biotinidase activity, individuals are classified as profound BD and partial BD. Patients with profound BD have less than 10% mean normal serum enzyme activity, whereas patients with partial BD have 10-30% of mean normal serum enzyme activity.

The most important differential diagnosis of BD is holocarboxylase synthetase deficiency. Holocarboxylase synthetase deficiency usually presents in newborn period but occasionally can also present in later childhood. Clinical symptoms including lethargy and hypotonia as well as biochemical changes including metabolic acidosis, lactic acidosis, hyperammonemia and organic aciduria are more severe as compared to that seen in BD. Optic atrophy, sensorineural hearing loss, myopathy and peripheral neuropathy seen in BD are not observed in holocarboxylase synthetase deficiency, thus are important clinical features that differentiate BD from holocarboxylase synthetase deficiency. Clinical and biochemical features of BD and holocarboxylase synthetase deficiency are compared in table 1.

TREATMENT OF BIOTINIDASE DEFICIENCY

Biotinidase deficiency is a very easily treatable metabolic disorder. Children with profound BD are treated with oral 5-20 mg of biotin per day independent of their age and weight. Most clinical symptoms resolve quickly after commencement of oral biotin. Seizures and ataxia resolve within hours to days and cutaneous manifestations resolve within weeks of commencement of treatment. Visual abnormalities, hearing loss and developmental delay once developed are usually irreversible even after treatment.

It must be emphasized to parents of children with BD that the treatment though is simple, but is life long and noncompliance to treatment whether intentional or unintentional would result in recurrence of symptoms within several weeks to months. Periodic assessment of BD patients by clinical geneticist including annual surveillance of vision and hearing evaluation is needed throughout life.

REFERENCES


