Review Article

Overview on Pathophysiology, Diagnosis, and Management of Biotinidase Deficiency in Pediatrics

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Abstract

A condition that interferes with the biotin cycle is known as biotinidase (BTD) deficiency. Endogenous biotin recycling is hampered, and different carboxylase deficits result depending on the amount of enzyme activity. There are two types of BTD insufficiency, which are determined by the amount of BTD Enzyme present in the serum. Pathogenic BTD gene mutations have been reported globally in a wide range of different ways. BTD deficiency is caused by complete and partial BTD gene mutations. The severe pathogenic disease is caused by profound BTD deficiency. Neuro-cutaneous symptoms are frequently evident in infants with significant deficiencies. Around the world, a significant percentage of neonates suffer from a partial deficiency. Although they are mostly asymptomatic, symptoms can sometimes arise under stressful circumstances. The treatment for symptomatic children or babies with positive screening results is lifelong oral biotin supplementation. The former may experience either a partial or full relief of symptoms. Results of neonatal screening programs confirm that postnatal biotin therapy shields patients with Biotinidase deficiency from symptoms. The article provides an overview of biotinidase deficiency in children, addresses programs for newborn screening for early detection and treatment of BTD-deficient infants, and explains how early treatment and proper patient care are facilitated by accurate diagnosis.

Keywords: Biotin, Biotinidase, Multiple carboxylase deficiency, Seizures

Introduction

Vitamins are essential parts of every person's daily molecular and chemical activities. Cofactors for reactions, hormones, antioxidants, and even eyesight, depend on them. Vitamin deficits may develop from inadequate environmental sources or from improper intracellular mechanisms for digesting vitamins. Biotin is a necessary vitamin that is received via food and is effectively recycled for additional usage. Patients suffer considerable morbidity and death when this recycling system malfunctions as a result of an enzyme shortage. It is inherited autosomal recessively and is referred to as Biotinidase Deficiency (BTD Deficiency) [1].

Biotin is known as vitamin B7 or vitamin H in humans. It dissolves in water. It serves as a coenzyme in the body for the carboxylation enzymes 3-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), acetyl-CoA carboxylase (ACC), and propionyl-CoA carboxylase (PCC). The task of releasing and recycling biotin from sources that are bonded to proteins and biocytin is carried out by the enzyme biotinidase (BTD). As a result of BTD's subsequent cleavage of the biocytin, biotin, and lysine are released. Biotin is a byproduct of holo-carboxylase's proteolytic digestion. Under physiological circumstances, BTD contains biotin-transferase activity, which allows biotin to be transported from biocytin to histone. BTD is a mammalian enzyme that is mostly present in the liver, kidney, and serum [2].

Because it is an autosomal recessive disorder, biotinidase deficiency (MIM #253260) inhibits the naturally occurring reprocessing and discharge of biotin from eaten proteins. Low biotin-dependent carboxylase activity and low levels of organic acid excretion in the urine are symptoms of BTD deficiency, which is also known as multiple carboxylase deficiency (MCD). BTD was once known as a late-onset MCD since the majority of patients' symptoms start to manifest after one month of age. The primary enzyme deficit in late-onset MCD was identified by Wolf *et al*. in 1982 as biotinidase. In late childhood or a few weeks after birth, the symptoms may manifest. In other circumstances, the patient may not exhibit any symptoms. The symptoms will lessen with the addition of biotin. BTD insufficiency is classified as

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either profound or partial, depending on the level of BTD present in the blood. With a mean activity of 7.1 nmol/min/L, BTD concentrations in human serum generally range from 4.4 to 10 nmol/min/mL. Significant BTD insufficiency is indicated by serum activity levels below 10% of normal. This kind creates MCD by cleaving endogenous biotin from biocytin, preventing a kid from recycling it **(Figure 1)**. Many countries check newborns at birth to assess the prevalence of the BTD syndrome and treat it with biotin supplements. An average serum activity of 10 to 30 percent BTD is referred to as a partial BTD deficiency in various populations. The patient who has a partial BTD deficit is often asymptomatic, although symptoms can appear under stressful conditions like fasting or viral infections [2].

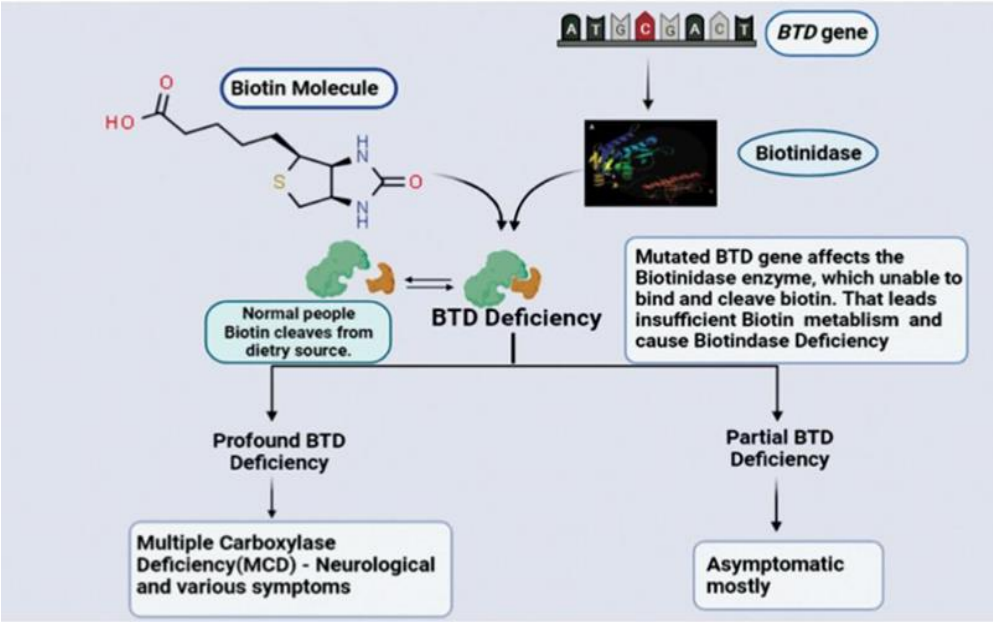

Figure 1. BTD insufficiency and inadequate biotin metabolism are caused by mutations in the BTD gene that affect the Biotinidase enzymes. Serum biotinidase levels are used to divide it into two categories: severe BTD deficit and moderate BTD deficiency [2].

In addition to neurological symptoms including hypotonia, seizures, developmental delay, hearing loss, and optic atrophy at a young age, patients with extensive BTD also present with cutaneous symptoms such as dermatitis, conjunctivitis, and baldness. If left untreated, people may have metabolic decompensation, a coma, or even pass away. Children with autism or developmental delay may be misdiagnosed with partial BTD, and patients with partial BTD often show milder symptoms under stress later in life. Although neurological deficits are permanent once they occur, therapeutic doses of biotin (5–20 mg daily) can prevent the symptoms of Biotinidase deficiency [3]. It's noteworthy to note that the mandatory newborn screening (NBS) programs in the US and some other countries successfully cure or prevent the signs of BTD deficiency by supplying medicinal doses of biotin supplements [4].

According to an early study on prenatal screening, BTD deficiency affects around 1 in 60,000 babies [5]. While incidence rates vary by country, higher frequencies have been observed in Saudi Arabia, Turkey, and Brazil [6-8]. BTD was thought to be rare in East Asia. Four instances of MCD were discovered among 606,380 infants in a Japanese newborn screening program that was being tested [9]. According to research from China, while screening 116,000 newborns failed to uncover any instances, selective screening of 9100 infants with suspected inborn metabolic abnormalities resulted in the identification of four children with BTD [10]. Six individuals with this disease were identified in a retrospective study of BTD conducted by Hsu *et al*. and their findings suggest that BTD continues to cause severe morbidity [3].

The article gives a general review of biotinidase deficiency in children, emphasizes programs for newborn screening for early detection and management of BTD-deficient neonates, and discusses how early treatment and proper patient care are facilitated by accurate diagnosis.

BTD Gene

The OMIM 609019 human BTD gene has been isolated and described. The manufacture of the BTD enzyme is controlled by the BTD gene, which is the only gene connected to BTD deficiency. There is one on chromosome 3q25. The cDNA hepatic library was used to get the human BTD cDNA. 543 amino acids with a molecular weight of 61,133 Da are encoded by the BTD cDNA. The total masses as a result of its highly prospective N-glycosylation sites range from 74 to

80 kDa. BTD has two potential AUG start codons and a 1629 bp open reading frame with respect to the first AUG. The presence of an intron between the two potential start codons may allow for alternative splicing. The first AUG start codon, which has 21 amino acids, and the second, which has 41 amino acids, have a reading frame overlap. Before amide cleavage or biotinyl transfer, one of the 13 cysteine residues in the BTD joins the biotinyl carboxyl group with a thiol ester, making it active [11].

In addition, the human BTD gene has three introns and four exons. Exons 1, 2, 3, and 4 are roughly 79 bp, 265 bp, 150 bp, and 1502 bp long, while the corresponding intron regions are >12.5 kb, 6.2 kb, and 0.7 kb in size, respectively. The first and second possible translation start codons are encoded by exons 1, respectively. Upstream of exons 1 and 2, the nucleotide sequence was examined for possible promoter elements. The promoter features found between 600 and 400 are in line with the broad expression of BTD, which demonstrates CpG island characteristics but lacks a TATA element. Thought to be necessary for TATAless promoter transcription initiation are the three initiators (INR) sequences and the six consensus methylation sites. The consensus sequence for the HNF-5 liver-specific transcription factor may be located at position 352. Exon 2's nucleotide sequence 5′ contains the second potential ATG start codon and includes a consensus sequence for the liver-specific transcription factor C/EBP within 300 bp of the 5′ ends of exon 2 [12]. Housekeeping genes share many of their traits with this sequence, but it also contains the second ATG start codon.

In connection with that, it was discovered that several sections of the human BTD amino acid sequence are highly conserved when it was compared to the amidases and nitrilases found in bacteria. The conserved areas are made up of the active cysteine sites of amidases and nitrilases, which probably point to the location of the BTD involved in binding biotin's thioester after its cleavage from biocytin. The pathogenicity of mutations can sometimes be predicted using in silico prediction methods and empirical data from the BTD enzyme activity, although the results are not always consistent. Understanding the relationship between a patient's genotype and biochemical phenotype requires the use of BTD gene sequencing [13].

BTD Mutation

BTD impairment might be severe or only partially absent as a result of gene mutations. BTD deficiency may be brought on by any of more than 300 pathogenic variations in the BTD gene. Intron and exon junctions are overlapping regions of the BTD gene that may be directly sequenced to assist in mutation analysis. There are several different BTD gene mutations, any of which can cause BTD insufficiency. Among the mutations are those resulting from premature stop codon formation or single amino acid replacement, compound allelic mutations, missense, nonsense, cryptic splice site mutations, single and multiple nucleotide insertions, single and multiple nucleotide deletions, and point mutations. A significant BTD deficit arises in the homozygous or heterozygous condition [14].

The whole coding sequence has also been discovered to have mutations, while exon 1 does not [14]. Although the entire BTD gene has been sequenced, including exon 1, in several published studies, the absence of a mutation in exon 1 is most likely explained by the presence of the first in-frame ATG in exon 1, as opposed to the second ATG, which is the preferred or only actually used initiation codon and is highly conserved. If this is the case, then we cannot anticipate that changes to exon 1 will influence BTD synthesis or secretion if the second ATG serves as the major or sole beginning site encoding the signal peptide sequence [15]. The main symptoms of BTD deficiency are abnormalities of the skin and nervous system [16]. Some BTD-deficient people do not exhibit a genotype-phenotype relationship [17]. The mutation in the protein's C-terminus is what results in the significant reduction of BTD activity [14]. Numerous missense mutations impact the carboxy terminus of the BTD gene, and these variants have the potential to cause severe deficiency [13].

Numerous BTD gene mutations are present in the American population. A review of several studies and publications on BTD deficiency reveals that a new BTD gene mutation consistently happens once every 10 years. Among the nations that reported many distinctive varieties were Turkey, France, the United Kingdom, Saudi Arabia, Austria, Hungary, Italy, Brazil, and China. Populations from India, Germany, Pakistan, Sri Lanka, Afghanistan, Iraq, Poland, Nigeria, Iran, Spain, Sweden, Egypt, Syria, and Ethiopia have all reported possessing the BTD gene mutation [2] on a global scale.

Clinical Manifestations of BTD Deficiency

Seizures, hypotonia, eating issues, developmental delays, hearing loss, ataxia, alopecia, and skin rashes are just a few of the neurological and dermatological symptoms that clinically untreated BTD patients may experience [5]. Examples of cutaneous symptoms brought on by immunological failure include skin rashes, eczema, alopecia, conjunctivitis, viral infections, and fungal infections [12]. The flexors and perioral regions have scaly, erythematous plaques and breakouts that resemble seborrheic dermatitis. In severe cases, open sores, lichenification, and crusting are evident. These sores may turn into secondary infections. Atypical lipid metabolism and alterations in skin composition in BTD patients can cause cutaneous complaints [17].

Symptoms can occasionally be mistaken for primary immunological deficits [18]. Recurrent viral or fungal infections are possible as a result of immunologic dysfunction. It is possible to identify respiratory issues such as apnea, stridor, and hyperventilation.

Some kids with BTD only exhibit one symptom, while other times they show a variety of cutaneous and neurological symptoms [19]. Oral biotin can be administered at therapeutic

levels to treat or prevent BTD symptoms. If auditory or visual problems do arise, they typically don't improve with oral biotin therapy [20]. Early biotin treatment can prevent hearing loss in children with substantial BTD identified by neonatal screening. The age at which symptoms first appear ranges from 2 weeks to 2 years, while some patients have illness signs much later in life [21]. Patients with a significant impairment who are untreated suffer sensor neural hearing loss in about 76% of cases. Patients with profound BTD begin to exhibit symptoms of the condition at a young age [22]. Without biotin treatment, impacted patients may have metabolic de-compensation, coma, or even death [23]. Seizures and hypotonia are the most prevalent neurological signs in patients with untreated severe insufficiency. Symptoms in patients with partial BTD are typically less severe [24]. Children with autism spectrum disorder and developmental delay may have the disease misdiagnosed. In a small percentage of untreated instances, stress may cause developmental signs such as hypotonia, dermatitis, and hair loss [25].

It can happen from infancy to adulthood. The symptoms can be mild, like a rash or baldness, or more severe, such as hypotonia, seizures, or developmental delay. Even after receiving biotin therapy, some symptoms may not improve, as is the case with profound BTD [26].

A common symptom of patients with profound BTD is seizures. In their case series, Venkataraman *et al*. reported seizure as the presenting symptom, with clonic seizure predominating [27]. Three of the twelve BD patients who had symptoms were found to have seizures by Canda *et al*. [28], but the majority of their patients had been identified by neonatal screening. Today, neonatal screening allows for early patient diagnosis. They receive oral biotin therapy. We rarely see symptomatic patients as a result of this [29].

In the study by Salbert *et al*. seizures were the primary symptom in 38% of the enzyme-deficient subjects, and seizures occurred in 43 of 78 (55%) symptomatic youngsters. The primary biotin-dependent carboxylases are subsequently compromised as a result of 27 BTD, and there is a buildup of potentially neurotoxic and epileptogenic compounds. According to in vitro studies in BTD fibroblasts, low biotin levels suppress both the activity of the enzyme holocarboxylase synthase (HCS) and the transcription of the HCS gene. Low levels of biotin, toxic metabolites such as organic acids, lactic acid, and biocytin, and hyperammonemia in BTD patients can cause a variety of neurological problems [30].

Salbert *et al*. [30] discovered ocular abnormalities in 51% of 78 BTD patients having symptoms. Infections accounted for 30% of the results, followed by ocular neuropathies (13%), motility issues (13%), alterations in retinal pigment (4%), and pupillary abnormalities (1%).27 Six patients had optic atrophy in both eyes, according to Hayati *et al*.'s summary of ocular symptoms of patients published from 1997 to 2011 in PubMed [31].

The spinal cord and optic nerves are primarily impacted by a group of demyelinating illnesses of the central nervous system known as neuromyelitis optica spectrum disorders (NMOSDs). In instances of NMOSD, biotinidase deficiency has been recognized as a diagnosis in the literature. In recent years, myelitis, spastic paresis, and paraplegia with or without retinal abnormalities have been recognized as significant impairments in older teens and adults. Transverse myelitis, multiple sclerosis, brainstem encephalitis, myasthenia gravis, and transverse myelitis are the most common false diagnoses for BTD patients. Patients with myelopathy, regardless of whether they had visual loss or not, should be aware of the late development of BTD, even if they had a partial response to steroid treatment [29].

It is crucial to understand that all of these symptoms can be treated with biotin and early detection to reverse them. However, if they do occur, developmental delay, hearing loss, and alterations in eyesight are permanent [32]. If patients are not given treatment, they may have metabolic de-compensation, coma, and death [33].

Radiological Findings of BTD Deficiency

Patients with BTD had T2 hyperintensities, extended extracranial spaces, basal ganglia calcifications, basal ganglion atrophy, ventriculomegaly, and expanded extracranial spaces. T2 and FLAIR hyper-intensities in the bilateral hippocampi and parahippocampal gyri were found by Bhat *et al*. as a novel discovery in BTD patients [34, 35]. Damage to the spinal cord has been seen, particularly in senior BTD patients [36].

Diagnosis

By screening newborns for the condition or testing patients who exhibit signs of the condition, Biotinidase deficiency is diagnosed. Serum and plasma contain measurements of enzyme activity. It is possible to undertake genetic testing to check for BTD mutations when enzyme levels are abnormal [37].

Through laboratory studies, high quantities of lactic acid and ammonia in the blood or urine might be found. Additional tests, such as arterial blood gas, serum amino acids, serum chemistry, etc., should be carried out when biotinidase deficiency is identified in a patient. Checks for organic acids and ketones may be performed on urine samples. Brain MRI imaging often shows cerebral edema, bilateral compensatory ventriculomegaly, and delayed myelination in patients who have been mistreated and are experiencing an acute crisis [38]. MRS (magnetic resonance spectroscopy) is used to evaluate the metabolic function of the brain. Although it is a rare tool, it might be useful in defining the type of brain pathology in vivo. Before and following the administration of biotin, changes in cerebral metabolic activity can be seen on

a positron emission tomography (PET) scan. An MRI scan might miss bilateral basal ganglia calcifications, but computer tomography (CT) scanning can detect them.

Recurrent fungal, viral, and skin infections should be thoroughly investigated for Biotinidase insufficiency. Electroencephalography (EEG) findings might range from rhythmic diffuse spike and wave discharges to diffuse polyspike discharges, and they usually return to normal after biotin therapy. A dilated fundoscopic examination can be carried out by an ophthalmologist to check for scotomata and optic nerve atrophy. The level of optic nerve damage in affected patients can be determined using visual evoked potentials (VEPs) and visual field tests [18].

Newborn-Screening

The first neonatal BTD screening program in Virginia was initiated in 1984 [39]. The first time dried blood samples from patients were used to gauge Biotinidase activity was in a pilot study in Virginia. BTD is screened for direct immunological testing, and findings are independent of dietary protein consumption. A significant percentage of false-positive results have been caused by immaturity and poor sample processing [40]. In term neonates, Biotinidase activity varies from 50 to 70% of adult serum Biotinidase activity, according to research by Wolf *et al*. The enzyme activity quickly increases to adult levels within a few days or weeks. Many countries check newborns for BTD.

False-positive findings may be seen in patients who have triglyceride levels that are too high, are on valproic acid, or have above-normal albumin levels. False negative results can arise when biotinyl-6-aminoquinoline is used as a substrate for sulfa medicines; happily, sulfa treatments are contraindicated in pregnant women and babies [12]. Results from newborn screening programs show that postnatal biotin treatment prevents the symptoms of BTD patients from appearing. Since newborn BTD screening programs began very recently after the first description of the condition, nothing is known about the disorder's long-term natural history [41].

Management of BTD Deficiency

Biotinidase deficiency is a lifelong ailment but is readily managed. Patients with severe BTD get daily doses of 5–20 mg of biotin. All symptomatic individuals who get biotin treatment have clinical improvement. The duration of seizures normally lasts a few hours to days, and the cutaneous symptoms also usually disappear within a few weeks. Treatment with oral biotin can alleviate the symptoms of alopecia, rash, ataxia, and developmental delay [29].

As the child grows, less biotin is given to him or her. Some individuals have tested the organic acid in their urine to assess whether the dosage of biotin is enough. As a consequence of the frequency of symptomatic partial BTD patients who were not screened and untreated patients who showed symptoms, the advice to treat partial BTD patients has expanded over time. Initial controversy surrounded the care of individuals with incomplete BTD [28].

Children that exhibit symptoms often have developmental delays and face the risk of permanently damaging their auditory, visual, or central nervous system functions. Children with significant BTD who were pre-symptomatically detected during newborn screening and treated with biotin supplements do not develop these negative effects [42]. Based on mutation analysis and Biotinidase enzyme activity, it is still uncertain whether or not an untreated patient will have symptoms. Patients are at a significant risk of developing illness symptoms if they participate in fewer than 1% of activities [43].

According to Wolf *et al*. children with BD should also have their psychomotor functioning evaluated, as well as a physical examination for neurological abnormalities, dermatological findings, and infections. Children with BD should also have their ophthalmologic examination (annually in deep BD, every two years in partial BD), as well as an ophthalmologic examination (annually in deep BD, every year in partial BD).

Even in high amounts, biotin is regarded as safe and non-toxic. This fact made medical professionals aware of a specific issue. The majority of clinical immunoassays that detect tiny amounts of analytics, such as hormones, rely on precise and sensitive biotin (avidin) technology [29].

The samples' high biotin content led to false aberrant results. Utilizing biotin may cause falsely elevated T3 and T4 levels as well as falsely low TSH levels, which could lead to a misleading diagnosis of hyperthyroidism. During follow-up, it should be remembered [44].

Pregnancy Management

Females with severe Biotinidase deficiencies who get biotin therapy have delivered healthy pregnancies and progeny. For a woman who is carrying a child with a biotinidase deficit or who is in danger of doing so, considering biotin supplementation for the mother is the only special pregnancy management option [45]. There is no established dosage for use during pregnancy [46].

CONCLUSION

An outstanding illustration of early identification and effective management of an inherited metabolic condition is Biotinidase deficiency. Oral biotin, a safe, widely accessible, and reasonably priced medication, is a simple and effective way to treat BDT deficiency symptoms in patients. It can be administered to symptomatic people, newborns who tested positive on screening, and moms who are at high risk of or have been previously diagnosed with BTD deficiency. Today, the majority of infants identified by newborn screening receive biotin treatment at a young age. For patients with

BTD deficiency, the NBS programs are life-saving. There is still a lot to learn about BD, as evidenced by the existence of late-onset patients with various clinical characteristics. We anticipate learning more about BTD deficiency as a result of the rising number of BD patients and the discovery of several mutations in the BTD gene.

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