BIOTINIDASE DEFICIENCY: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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Introduction

Biotinidase deficiency (**BTD**) is a rare neurocutaneous disorder inherited by an autosomal recessive gene in which the enzyme biotinidase is defective. Consequently, the vitamin biotin is not produced from biocytine. Clinical manifestations of patients with BTD can appear at any timepoint from infancy to adulthood. Various neurological, ophthalmological and dermatological symptoms may occur in not treated patients with BTD, such as epilepsy, ataxia, developmental delay, hearing loss, alopecia and skin rashes [1-3]. Many of the above symptoms can be alleviated if supplementation with biotin is initiated at an early stage of the disease [3, 4]. However, deficiencies of hearing and vision may persist even after the initiation of oral biotin therapy [5].

Pathogenesis

The activity of the enzyme biotinidase, which is responsible for the recycle of biotin, is reduced to a lesser or bigger extent due to mutations in the BTD (biotin cycle, figure 1) [4, 6, 7]. Patients with this defect eventually progress to suffer from biotin deficiency. Based on the biotin cycle this deficiency will finally result in impaired activity of the carboxylases which are biotin-dependent and also high quantity

Figure 1. The Biotin Cycle
Wolf B.Mol Genet Metab 2011; 104: 27-34

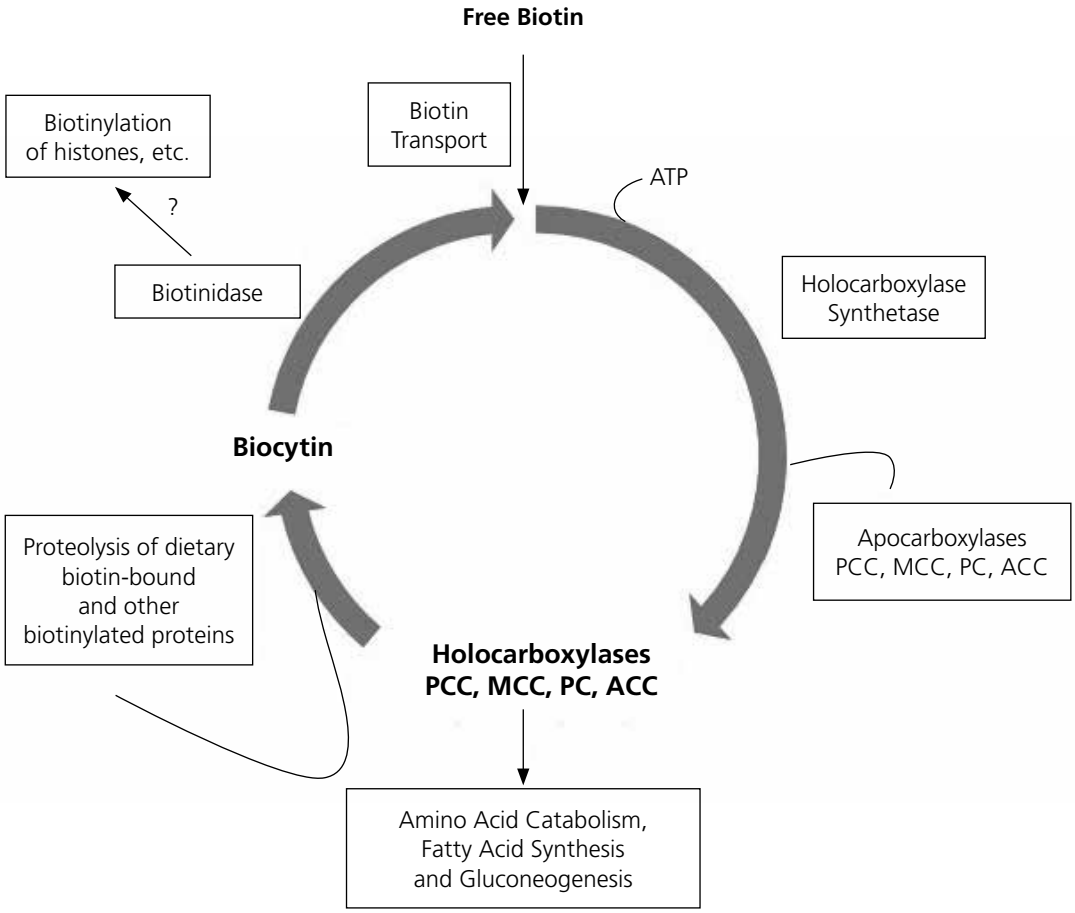

Table 1. The most frequent and occasional symptoms reported especially for profound cases of BTD

Symptom	Prevalence
Seizures	Frequent
Hypotonia	Frequent
Hearing loss	Frequent
Skin rashes (eczema)	Frequent
Hyperventilation, laryngeal stridor, and apnea	Occasional
Optic atrophy	Occasional
Developmental delay	Occasional
Hair loss (alopecia)	Occasional
Conjunctivitis	Occasional
Limb muscle weakness	Occasional
Myelopathy	Occasional
Recurrent viral infections	Occasional
Fungal infections (candidiasis)	Occasional
Ataxia	Occasional
Scotoma	Occasional
Spastic paraparesis	Occasional
Lethargy	Occasional

of related organic acids will be accumulated. These metabolic alterations could lead to ketolactic acidosis and hyperammonemia [8, 9].

Clinical characteristics

The clinical characteristics of patients with biotinidase deficiency usually vary regarding the extent of serum biotinidase activity. When biotinidase activity is reduced to 10-30% of mean normal, this condition is referred to as partial BTD, whereas when the enzyme activity is less than 10% of mean normal values these patients have profound BTD which is the more severe form of the disease [4]. If a clinician does not recognize and treats early enough this condition, its symptoms usually appear within the first few months of life, although it can also become obvious in late childhood or even in adult life [5, 10].

Most of the symptoms of BTD can be alleviated or prevented with pharmacological doses of oral biotin, specifically at a starting dose of 5-10 mg/d of free biotin, although higher daily doses may be required for some patients [9, 11]. However, if various clinical characteristics such as auditory and visual defects are observed these symptoms are usually irreversible even with biotin therapy per os [5]. If infants with profound BTD are detected with screening test and treatment is initiated soon after delivery, hearing loss can be prevented. The onset of symptoms varies from several weeks after birth to the first two years of age, although several patients may present symptoms later during life (adult forms of BTD) [4, 12].

The systems and organs of the objects with BTD that are mostly affected, especially when not treated properly are the skin, the eyes and brain functions [1-3]. Children with BTD manifest a single symptom or sometimes present with multiple neurological and dermatological findings [13, 14]. The following table summarizes the most frequent and the occasional clinical characteristics that are described in children with profound BTD (Table 1) [4, 15, 16].

Seizures are a common symptom of patients with profound BTD, although adult neurologists do not often encounter symptomatic patients, because of the early screening of the disease and the appropriate treatment [17, 18]. The most common type of seizures are generalized tonic-clonic (56%), but there have also been reported myoclonic seizures, infantile spasms, or even Ohtahara syndrome [19]. As regard to pathophysiology, it seems that due to absence of the recycling of biotin, consequently there is an accumulation of metabolites which are potentially neurotoxic and epileptogenic [3, 6, 20].

As in regard to other neurological symptoms, lately adults with profound form of BTD have been referred to physicians with symptoms like myelitis, spastic

BOX 1.

- 2-3 ml of whole blood should be obtained in a sodium or lithium heparin tube.
- Immediately or until 1 hour after collection, blood should be centrifuged to collect the serum sample and stored at -80°C until testing.
- The sample should be transported with dry ice.
- For the screening of newborns a completely dried blood spot along with the parents' samples are required.

Table 2. Laboratory values for biotinidase enzyme activity (adapted from [31])

Category	Mean activity ± SD (nmol/min/ml serum)
Normal values	7.57 ± 1.41
Heterozygotes	3.49 ± 0.72
Symptomatic individuals	0.12 ± 0.18
Newborn screening	0.19 ± 0.16
Individuals with partial BTD	1.47 ± 0.41

paraparesis or paraplegia and optic neuropathies. The above clinical findings are mimicking the symptoms of the demyelinating diseases known as neuromyelitis optica spectrum disorders (NMOSD) [21, 22]. Many cases of BTD in the literature have been reported that may be misdiagnosed as multiple sclerosis, NMOSD, myasthenia gravis, myelitis or atypical encephalitis [17, 21]. Adult cases of BTD should be considered for patients presenting with myelopathy with or without loss of vision even if there have been limited responsiveness to steroid therapy [14, 17, 22].

Many of the clinical symptoms of BTD and especially the dermatological findings are attributed to immunological dysfunction [8, 13, 23]. Sometimes symptoms can mimic conditions like primary immune deficiencies and this can disorientate the differential diagnosis [24].

Of note, several adults with profound BTD may remain asymptomatic through the course of the disease even without treatment and there is no certain explanation for this observation [25], though an any timepoint someone can develop symptoms. A possible theory is that there may be epigenetic factors that protect patients from developing symptoms [8, 26, 27]. Another probable explanation for the variations of the clinical findings in different individuals are the differences in biotinidase Km variants, which are reported in literature [28].

Patients with partial BTD usually have milder symptoms. The diagnosis of the disease may be misleading in cases of children with developmental delay and autism [2, 12, 18].

Diagnosis

The diagnosis of BTD is established by measuring biotinidase activity. Radioassay method is used to measure the enzyme activity in collected samples, especially serum or plasma. The activity can be estimated also in other tissues, like leukocytes or fibroblasts but these measurements could be less reliable [25, 29]. Sample collection should be performed according to laboratory guidance by physicians when requested. Usually 2-3 ml of whole blood should be obtained in a sodium or lithium heparin tube. Immediately or until 1 hour after collection, blood should be centrifuged to collect the serum sample and stored at -80°C until testing. The sample should be transported with dry ice, because storing samples at -20°C has been shown to diminish the biotinidase activity. For the screening of newborns a completely dried blood spot along with the parents' samples are enough to determine the laboratory diagnosis (BOX 1).

Only when testing for DNA samples shipments should be done in ambient conditions as soon as possible. The range of values from normal to several cases of BTD are shown in table 2 [7, 20, 25, 30, 31].

The enzyme analysis could show vague results regarding the asymptomatic carriers of the disease and those with partial BTD, rendering the laboratory diagnosis equivocal. In such cases and in individuals with heterozygosity genetic testing could provide better information for establishing the diagnosis [18, 26, 27, 30].

Other biochemical testing, in patients with no treatment, that could help reinforce the diagnosis may be the elevated levels of metabolic ketoacids, lactic acids and high ammonia levels [7, 8, 32].

Management

As mentioned above, initial treatment of patients

with profound BTD is with 5 mg/day supplementation of oral free biotin, but dose can be adjusted in regard to clinical outcome up to 20mg/day. All individuals presenting with symptoms of the disease tend to show clinical improvement with biotin therapy. The frequent symptom of seizure usually resolves instantly (hours or days) after treatment initiation and also skin lesions alleviate within weeks. Apart from that, other symptoms such as alopecia, ataxia, and developmental delay can improve overtime if biotin therapy per os is started in the early stages of the disease [29, 33, 34].

Treatment of partial BTD was initially controversial, but over the years, due to the appearance of patients with no treatment developing symptoms, it is strongly recommended nowadays that treatment should be applied also in cases of partial BTD [10, 16].

Screening of newborn has provided much help for the prevention of symptoms, because it has been shown that initiating treatment in yet asymptomatic children with this condition could reverse defects such as hearing loss, optic atrophy and brain dysfunction, whereas children suffering from BTD often present with these symptoms. Currently it is unclear whether patients not receiving treatment will develop symptoms or not and there is no clear prognostic factor of the disease [29, 34, 35]. From literature it is known only that patients with very low enzyme activity (<1%) appear to have high risk for presenting with symptoms of BTD.

It is strongly recommended that children with both profound and partial BTD should be evaluated for psychomotor deficits and for hearing loss periodically, and have ophthalmologic and physical testing for neurological defects, cutaneous lesions and viral or fungal infections [33]. Another parameter that should be examined is the dose of oral biotin. In a recent study, hair loss during adolescence was diminished in two girls with profound form of BTD after increasing the dosage of oral biotin [33, 35]. More data is needed in order to determine the dosage of biotin that is mandatory for children with BTD [1, 12, 23].

Oral biotin seems to have a good pharmacokinetic profile and it has not shown until now serious adverse events even when administered in high doses. Nevertheless, samples with high doses of biotin can cause incorrect results, such as false elevated levels of thyroid gland hormones (T3 and T4) and false low TSH measurements, misleading the diagnosis to hyperthyroidism. This should be considered during follow-up [36].

Conclusion

BTD is a relatively rare inherited metabolic disorder, whose early recognition can lead to successful treatment and in turn to disability prevention. Affected patients with BTD can be easily treated with supplementation of oral biotin and this treatment reverts most of the symptoms. Nowadays, newborn screening for this condition, that is applied in many countries worldwide has offered a lot to the early recognition of the disease. Apart from that, due to the reversibility of several of the symptoms the number of patients with no symptoms is rising. Early initiation of treatment in such cases is crucial for the best clinical outcome. On the contrary, the appearance of adults with BTD and various clinical characteristics designates that there are still many mechanisms to be examined and much to be learned about BTD. Based on the increasing number of patients with BTD and the detection of many mutations in the responsible gene, we expect to collect more data in the future about correlation between the genotype and the phenotype of the disease. The diagnosis of BTD should be taken into consideration by clinical pediatricians and neurologists in rare cases where differential diagnosis relates to the clinical characteristics, mainly regarding neurological and dermatological manifestations.

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