BIOTINIDASE DEFICIENCY

Biotinidase deficiency (Online Mendelian Inheritance in Man [OMIM] database No. 253260) is a disorder of biotin recycling. Biotin is a water-soluble vitamin of the B complex that acts as a coenzyme in each of 4 carboxylases in humans (pyruvate carboxylase, propionyl-coenzyme A [CoA] carboxylase, β-methylcrotonyl CoA carboxylase, and acetyl-CoA carboxylase). Missing a diagnosis of biotinidase deficiency, a condition that is easily treated with vitamin supplementation, can have severe consequences, including seizures, developmental delay, and sensorineural deafness.

Incidence

Neonatal screening for biotinidase deficiency has been instituted in many states (25 at the time of this publication) as well as many countries (approximately 25) since the biochemical basis was elucidated by Wolf et al in 1983. Of slightly more than 8.5 million newborn infants screened worldwide up to 1990, 142 affected infants have been identified, with 76 having profound (<10% activity) deficiency (approximate incidence 1 in 112000) and 66 having partial (10%–30% activity) deficiency (approximate incidence 1 in 129000). Most affected individuals who have been identified are of European descent; however, individuals of Turkish, Saudi Arabian, and Japanese descent have been described.

Clinical Manifestations

Biotinidase deficiency can present with clinical symptoms as early as the first week of life up to 10 years of age. Most infants first exhibit clinical symptoms between 3 and 6 months of age. The most commonly affected systems are the central nervous system and skin. Affected children usually have myoclonic seizures, hypotonia, seborrheic or atopic dermatitis, partial or complete alopecia, and conjunctivitis. Other features may include developmental delay, sensorineural hearing loss, lethargy, ataxia, breathing problems, hepatosplenomegaly, and coma. Laboratory findings vary and can include ketolactic acidosis, organic aciduria, and mild hyperammonemia.

Individuals with partial biotinidase deficiency can present with skin manifestations and no neurologic symptoms. Several children with profound deficiency have presented later in childhood or during adolescence with hemiparesis and eye findings (scotoma). With therapy, the eye problems resolved quickly, but the neurologic findings remained for a longer period of time. There are even reports of adults with profound biotinidase deficiency who have never had symptoms but were diagnosed because their children had positive results of newborn screening.

Pathophysiology

Each of the 4 carboxylases in humans requires biotin as a cofactor. The carboxylases are first synthesized as inactive apoenzymes. After synthesis, biotin is added to the inactive proteins through 2 partial reactions, each of which is catalyzed by the enzyme holocarboxylase synthetase. Ultimately, each of these active, biotin-containing enzymes is degraded. The biotin-containing products of degradation are acted on by biotinidase to liberate biotin, which is recycled and enters the free-biotin pool. Biotinidase deficiency
results in inability to recycle endogenous biotin and to release dietary protein-bound biotin. Thus, the brain may be unable to recycle biotin adequately. This may lead to dependence on the biotin that crosses the blood-brain barrier, resulting in decreased pyruvate carboxylase activity in the brain and accumulation of lactate. The neurologic symptoms may be secondary to accumulation of lactic acid in the brain.²

Inheritance

Biotinidase deficiency is inherited as an autosomal recessive trait. The biotinidase (BTD) gene has been mapped (chromosome 3p25), cloned, and characterized.¹²⁻¹⁴ Sixty-two mutations of the BTD gene have been described to date.¹⁴ Interestingly, when testing a US population, mutations occur at different frequencies in children with symptoms than in children who were only identified through newborn screening. Two mutations accounted for 52% of the mutations found in symptomatic patients, and 3 other mutations accounted for 52% of mutations in children identified through newborn screening. Partial BTD deficiency is predominantly caused by the 1330G→C mutation on one allele in combination with one of the mutations causing profound deficiency on the other allele.¹⁴

Benefits of Newborn Screening

Biotinidase deficiency has been identified as an appropriate disorder for newborn screening by numerous countries and states because of its prevalence, the potentially tragic outcome if not diagnosed, and availability of effective, low-cost treatment. Unfortunately, once symptoms have occurred, some of the findings are not reversible with therapy. This is particularly true in the case of the neurologic findings. For example, sensorineural hearing loss is common (detected in approximately 75% of symptomatic children with profound deficiency) and is usually irreversible.⁶

Screening

The best method of screening is a semiquantitative colorimetric assessment of biotinidase activity that can be performed on whole blood spotted on filter paper.²,¹⁵,¹⁶ Although the majority (>80%) of patients with biotinidase deficiency demonstrate organic aciduria when symptomatic, a significant percentage (20% in one study) may not; therefore, tandem mass spectrometry (MS/MS) testing should not be used for newborn screening of biotinidase deficiency.²

Follow-up and Diagnostic Testing

A positive screening result for biotinidase deficiency should be followed up with definitive testing for diagnosis. Quantitative measurement of enzyme activity should be performed on a fresh serum sample. Residual enzyme activity determines whether the patient has profound (<10% activity) or partial (10%–30% activity) biotinidase deficiency. Most patients with profound deficiency present early in life, whereas those with partial deficiency can present later or with a cutaneous phenotype and no neurologic findings.
Brief Overview of Disease Management

Children with profound biotinidase deficiency have been treated successfully with biotin. Pharmacologic doses of biotin (5–20 mg/day) were determined empirically.⁸,¹⁷ One patient required a dose of 30 mg/day to resolve dermatitis.¹⁰ For most patients, the currently prescribed dose is probably much more than is needed to overcome the deficiency. It should be stressed that the biotin must be in the free, not bound, form to be effective. There are no known adverse effects of the currently recommended dosage of 5 to 20 mg/day.¹⁹

Once therapy is instituted, cutaneous symptoms resolve quickly, as do seizures and ataxia. Some of the symptoms (as mentioned previously) are less reversible, including hearing loss and optic atrophy. Children who have developmental delay have been noted in some cases to achieve new milestones and regain lost milestones after beginning therapy.¹⁵ There are individuals reported who have profound biotinidase deficiency, have never been treated, and have never had any associated symptoms.¹¹

Partial biotinidase deficiency can probably be treated with lower doses of biotin (1–5 mg/day) and/or only during times of metabolic stress.¹⁹ There are children with partial deficiency who have never had any related illness. In others with partial deficiency, it has been noted that mild intercurrent illnesses such as gastroenteritis can lead to development of typical clinical symptoms that resolve with biotin therapy.¹⁹

Current Controversies

As noted above, it is difficult to determine if individuals with partial biotinidase deficiency need daily therapy. When such individuals are identified in newborn screening programs, follow-up happens routinely and care is instituted. The negative psychological aspects of learning through newborn screening that an infant potentially has a genetic disorder and the parental anxiety generated should be weighed against the positive aspects, including that the treatment is simple and inexpensive and some individuals with partial deficiency would (at some point) have symptoms. Although this is mildly controversial, it is truly not of enough significance to negate the value of newborn screening for the disorder.
REFERENCES


