

Biotinidase Deficiency

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Outcome without screening:

Biotinidase deficiency is an autosomal recessive, inherited disorder. When untreated a patient will usually present with a combination of neurologic and cutaneous symptoms. The neurologic signs most often include hypotonia and seizures. Over three-quarters of symptomatic patients have hearing loss. Cutaneous symptoms may present as rashes and alopecia. Recurrent infections occur. Associated acute onset symptoms have included acidemia, organic aciduria, and hyperammonemia. Two categories of deficiencies are recognized: profound, and partial. Symptoms have presented within 1 week to 10 years of age.

Incidence:

Both the profound and partial deficiency cases occur in about 1/61,000 births, as detected by newborn screening programs. Each is inherited as an autosomal recessive disorder, with both parents being obligate carriers, and their having a 1/4 or 25% chance of recurrence in future pregnancies of a similarly affected child.

Outcome with screening:

Patients with both types of biotinidase deficiency detected by newborn screening have generally been treated with biotin replacement. Patients who have been treated with biotin who have never been symptomatic have development normally. All symptomatic patients placed on treatment for biotinidase deficiency have improved.

Causes of Biotinidase Deficiency:

The clinical symptoms appear to be caused by the deficiency of biotinidase, due to mutations in the *BTD* gene. The enzyme hydrolyzes a peptide bond from the compound biocytin, thus releasing biotin to be reutilized in four enzyme reactions. Biotin is a cofactor in these enzyme reactions. Therefore, biotinidase deficiency causes a relative decrease of endogenous biotin available for these enzyme reactions to occur efficiently. While exogenous biotin is present from the diet, the body depends on this recycling of endogenous biotin for normal function. There are 5 mutations in the *BTD* gene that are present in about 60% of the profound biotinidase deficiency alleles.

Screening test and confirmation:

Biotinidase activity is measured from the blood filter paper spot with a colorimetric test. This measures the release of p-aminobenzoate from N-biotinyl-p-aminobenzoate. If the level falls below the cut-off set by the state lab, a repeat specimen may need to be obtained, or a quantitative enzyme test may need to be performed by the state designated genetic center. If confirmed deficiency occurs, there are categories of patients that relate to outcome. *Profound biotinidase deficiency* occurs when the patients sera/plasma has <10% normal mean biotinidase activity in an experienced laboratory. Values between 10-30% of normal mean activity are

termed *partial biotinidase deficiency*. Further molecular testing is clinically available for the mutant alleles described above.

Newborn Screening Considerations

False positive results (obtaining low or absent activity) may occur in premature babies whose levels have not reached term newborn ranges, and by the placement of newborn screen filter papers in a plastic bag prior to drying.

Treatment:

Treatment consists of replacing biotin orally, usually 5-10 mg/day. Dietary limitations or replacements are not indicated in biotinidase deficiency.

Special concerns and issues:

Biotinidase deficiency was described only in the past 2 decades and a newborn screening test quickly devised. Therefore knowledge of the clinical symptoms has come primarily from patients not detected by newborn screening programs and by symptoms. While the partial biotinidase deficiency patients were not originally treated, rare clinical symptoms have occurred, and now it is recommended to treat both groups of patients.

If a patient does have symptoms, treatment is recommended. However, some symptoms have recurred while on treatment. For those patients who have been detected by newborn screening and have never exhibited symptoms, symptoms are not likely to occur. Some patients have responded quickly to treatment, while others, especially those in whom a long time has elapsed between the onset of symptoms and treatment, may resolve symptoms over a more protracted period of time.