



Biotinidase Deficiency Information

Biotinidase is an enzyme that releases biotin, an essential vitamin cofactor, from a bound form so that it can be used by the body. Deficiency of the enzyme results in improper functioning of several other enzyme systems dependent on biotin, leading to neurological damage. This recessively inherited disorder affects the regeneration of biotin and leads to greatly reduced carboxylase activity. The incidence is estimated at 1:72,000 to 1:126,000 live births. However the prevalence in Nebraska has been higher than this. For example between 2001 and 2004 newborns with profound or partial deficiency were found in about 1:7000 births.

Clinical Features:

The symptoms of biotinidase deficiency are variable with respect to age of onset, frequency and severity. Infants with biotinidase deficiency appear normal at birth but develop one or more of the following symptoms after the first few weeks or months of life: ataxia, seizures, hearing loss, alopecia, developmental delay, skin rash, or metabolic acidosis which can result in coma and death. Individuals with partial deficiency (a variant form) may also be at risk for development of symptoms. Family studies are indicated when an affected newborn is identified.

Laboratory Tests:

Enzyme activity quantitated using a colorimetric assay. In the presence of the enzyme, a color change occurs. Positive results reflex to DNA for some of the common mutations associated with biotinidase deficiency.

TEST RESULTS	LIKELY CAUSES	ACTIONS TO TAKE WHEN POSITIVE RESULT FOUND
≤ 8.0 (Presumptive Positive) ----- 8.1 - 16 (Presumptive Positive Borderline Range)	Biotinidase deficiency False positive Heat denatured specimen ----- Biotinidase deficiency Partial deficiency Carrier False positive Heat denatured specimen	For both scenarios (presumptive positive or presumptive positive borderline range) Laboratory immediately notifies via phone and fax (followed in writing) submitter, newborn's physician and NNSP. Newborn's physician assesses condition of newborn and orders repeat tests as appropriate.

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Confirmation and Treatment:

Consultation with a pediatric metabolic specialist should be made for confirmation and diagnosis (see Biotinidase ACT Sheet,).

- Upon notification of an initial positive screening result between 8.1 – 16 ERU, physician should collect or cause to be collected a repeat filter paper specimen. If on repeat, the enzyme activity continues to be 16 or below, and reflex DNA shows any pattern besides 2 copies of the D444H, immediately move to confirmatory testing (See ACT sheet).

- If the initial result is ≤ 8.0 ERU move directly to confirmatory testing (See ACT sheet). The acute symptoms of biotinidase deficiency will completely disappear with administration of pharmacological doses of biotin. If given early enough in an infant's life, the prognosis for normal growth and development is good. If children are not detected until neurological damage has occurred, treatment with biotin can reduce further damage but not reverse the neurological damage already done.

Screening Practice Considerations:

Detection of the deficiency does not depend on timing or type of feeding because it is an enzyme test. It should therefore be detected on the first specimen unless the infant has been transfused with whole blood, plasma, or serum. ALWAYS OBTAIN A NEWBORN SCREENING SPECIMEN PRIOR TO A TRANSFUSION. The enzyme is prone to damage if the sample is delayed in shipping or exposed to high temperatures resulting in a potentially false negative test.

Special Considerations:

If on the repeat filter paper specimen the enzyme continues to be 16 or below the laboratory will reflex the specimen to DNA. If the DNA shows two copies of D444H, this genotype is commonly associated with very mildly affected partial biotinidase deficiency, and the metabolic specialists will recommend the RDA ADEK vitamins, until chewable multivitamins with RDA biotin can be administered. No pharmaceutical dose of biotin is recommended for these cases. Prompt confirmatory testing is required even if there is evidence to suggest that one of the situations associated with false positive screens is present. These situations can include prematurity, heat-damaged specimen, or hyperalimentation. The presence of any of these does not exclude the possibility of disease.