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## Biotinidase Deficiency

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**Synonyms and related keywords:** infantile multiple carboxylase deficiency, juvenile carboxylase deficiency, late-onset deficiency, deficiency of free biotin, abnormalities in fatty acid synthesis, abnormal amino acid catabolism, abnormal holocarboxylase synthetase deficiency

### AUTHOR INFORMATION

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### Disclosure

### INTRODUCTION

Section 2

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**Background:** Biotinidase is a ubiquitous mammalian cell enzyme occurring at high levels in the kidney. The primary function is to cleave biotin from biocytin, preserving the pool of biotin for u

biotin dependent enzymes, namely the 4 human carboxylases.

Multiple carboxylase deficiency responsive to biotin administration was first described in 1971. Further characterized the infantile form of multiple carboxylase deficiency as biotinidase deficiency. Neonatal period is the usual period of presentation for multiple carboxylase deficiency, and this is due to biotinidase deficiency.

Disease caused by complete or partial absence of the enzyme is associated with a wide spectrum of manifestations, including abnormalities of the neurological, dermatological, immunological, and endocrine systems. In spite of its rarity, early recognition is crucial because expeditious treatment may reverse the manifestations.

**Pathophysiology:** Biotin is an imidazole derivative found in many natural foods. Bacteria in the gut produce large amounts of human biotin. It serves as a cofactor for human carboxylases, including pyruvate carboxylase, propionyl-coenzyme A (CoA) carboxylase, beta-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase.

Biotin is covalently bound to these enzymes. Under normal conditions it undergoes proteolytic cleavage to biocytin or biotinyl peptides. Cleavage of these breakdown products results in restoration of free biotin cofactor functioning. Biotinidase affects this cleavage and its absence or deficiency impairs this process, leading to a deficiency of free biotin and slowing the functioning of the biotin-dependent carboxylases. The enzyme plays important roles in intermediary metabolism and impairment causes abnormalities in fatty acid synthesis and catabolism, and gluconeogenesis. These abnormalities may manifest in a variety of clinical signs and symptoms which are presented below.

Biotinidase deficiency typically accounts for the so-called late-onset multiple carboxylase deficiency. Neonatal onset of multiple carboxylase deficiency is more likely due to another biotin-responsive abnormality, holocarboxylase synthetase deficiency. This enzyme is responsible for covalently binding biotin to the various apocarboxylases. The defect occurs in the Michaelis constant values of biotin, requiring large amounts of free biotin to ensure binding.

### Frequency:

- **In the US:** The incidence of profound biotinidase deficiency is estimated at 1:137, 401. The incidence of partial and profound deficiencies is 1:61, 067. In Virginia in 1986, Heard and colleagues determined that neonatal screening was cost effective. Now screening for biotinidase deficiency is routinely performed in several states and around the world.

**Mortality/Morbidity:** If treated promptly, biotinidase deficiency may be asymptomatic. Prolonged institution of biotin therapy may leave the patient with varying degrees of neurological sequelae including mental retardation, seizures, and coma. Death may result from untreated profound biotinidase deficiency.

**Sex:** Males and females appear to be affected equally, which is consistent with an autosomal recessive inheritance.

**Age:** Profound biotinidase deficiency (<10% of normal serum enzyme activity) typically presents within the first months of life, though presentation in the neonatal period or after the first decade occurs.

**CLINICAL****Section 3**

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**History:**

- Partial biotinidase deficiency (10-30% of mean normal activity) is associated with an increased risk of developing the same symptoms that affect children with profound deficiency. However, the onset of symptoms seems to be associated with metabolic stressors (eg, illness, fever, fasting), and patients may not be symptomatic until such time.
  - This propensity to metabolic deterioration during stress may be a useful clue in the diagnosis of the deficiency, though it also is a feature of other inborn errors of metabolism. Symptoms are responsive to biotin administration.
  - Sudden death is reported in association with presumed biotinidase deficiency, possibly due to brain stem dysfunction. Therefore, include biotinidase deficiency in the evaluation of sudden death syndrome, especially when other family members have possible clinical manifestations of biotinidase deficiency.
  - The spectrum of clinical signs and symptoms is varied. Consider biotinidase deficiency in the differential diagnosis of intractable seizures, acidosis, rash, or failure to thrive.
- Seizures
  - In a recent retrospective study, 38% of patients with biotinidase deficiency presented with seizures in combination with other features of the disorder. Approximately 55% of these patients had seizures at some time during the period of review. Seizures most frequently were generalized, though myoclonic and infantile spasms were noted in a significant percentage.
  - Seizures and other manifestations typically are not responsive to conventional therapy but are responsive to pharmacological dosing of biotin.
- Other neurological sequelae
  - Developmental delay
  - Ataxia
  - Neuropathy
  - Auditory nerve dysfunction
  - Biotinidase deficiency rarely presents as spastic paraparesis.
  - Although most symptoms respond well to administration of biotin, severe permanent neurological damage can result from untreated biotinidase deficiency.
  - Permanent ophthalmological and audiological injury recalcitrant to biotin therapy also can occur.

- Immunological deficiencies
  - Chronic and possibly lethal fungal infections characterize immunological deficiencies.
  - Cellular immunity abnormalities possibly are due to accumulation of toxic metabolites.
  - The immunological dysfunction is ameliorated with biotin treatment.
- Breathing abnormalities
  - These are common and include apnea, hyperventilation, and laryngeal stridor.
  - Stridor and breathing pattern abnormalities possibly are due to dysfunction of medullary centers affected by the metabolic disorder. This may lead to other bulbar symptoms: difficulties.

### **Physical:**

- Eye: Perform a detailed ophthalmological examination to find evidence of optic atrophy.
- Skin
  - Dermatological manifestations are particularly striking when they occur and include eczematous, scaly perioral/facial rash. Distribution of the rash is described as periorificial propensity to affect areas surrounding the body orifices. Rashes may be mistaken for allergic deficiency. For this reason, recalcitrance to conventional therapy for skin rashes should consider an inborn error of metabolism, including biotinidase deficiency.
  - Alopecia with loss of hair color also occurs.
  - Intriguingly, these dermatological findings may be attributable to abnormal fatty acid metabolism, possibly due to the secondary carboxylase dysfunction.
  - Although they may be severe, the rash and alopecia typically respond rapidly to biotin over days to months.
  - Chronic candidiasis may occur.
- Neurodevelopmental effects
  - Hypotonia and developmental delay are manifestations in infancy
  - Presentation in older children includes ataxia and developmental delay
  - Optic atrophy and audiological deficits occur as isolated signs or in association with

### **Causes:**

- The gene that encodes biotinidase is localized at band 3p25.
- A common mutation, which is present in approximately one half of symptomatic children,
- A second, less common mutation, Arg538 to Cys, also has been described.

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## DIFFERENTIALS

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### Other Problems to be Considered:

Consider sepsis, meningitis, or toxic exposure in a child who presents in extremis with intracta metabolic disruption.

If laboratory testing indicates hyperammonemia and/or acidosis, other inborn errors of metabo

Neonatal-onset symptoms of biotinidase deficiency may be difficult to differentiate from holoca deficiency (see [Pathophysiology](#)) and also responds clinically to administration of biotin.

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## WORKUP

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### Lab Studies:

- Upon presentation, obtain laboratory studies to determine if an inborn error of metabolism below.
- Illness or catabolic stress may cause metabolic disruption, and the performance of labor: to the etiology of the disorder.
- Obtaining samples during the illness is important because these clues may disappear in one with partial enzyme deficiency.
- Specific tests
  - Serum ammonia
  - Urine organic acids
  - Plasma amino acids
  - Urine ketones
  - Blood gas

- Serum chemistries
- Biotinidase, carnitine, and acylcarnitine profiles

### **Imaging Studies:**

- MRI is the neuroimaging study of choice for the evaluation of a child with a possible inborn biotinidase deficiency may demonstrate cerebral edema, low attenuation of white matter, ventricular enlargement.
- Magnetic resonance spectroscopy also helps determine the functional metabolism of the techniques and using them may help to delineate the nature of the brain disorder in vivo.
- Positron emission tomography is used in an experimental setting to demonstrate the change and after biotin therapy.
- CT scan may demonstrate bilateral basal ganglia calcifications that may not be as readily

### **Other Tests:**

- Ophthalmologic testing
  - An experienced ophthalmologist should perform a dilated fundusoscopic examination
  - Visual field testing and visual evoked potentials may help to determine the degree of
- Audiologic testing
  - Perform audiologic testing in all children because hearing deficits in symptomatic children after treatment.
  - Brainstem auditory evoked potentials may help to delineate the abnormality in your patients.
- Electroencephalography
  - EEG findings prior to treatment demonstrate poor organization of background and
  - Frequent focal spikes were observed in 1 child during the interictal period.
  - Ictal manifestations were well described in 1 report, demonstrating diffuse polyspike (myoclonic) followed by the appearance of rhythmic diffuse spike and wave discharge generalized tonic-clonic seizure.
  - EEG findings are variable and may normalize completely after therapy.

**Histologic Findings:** Pathological lesions in biotinidase deficiency vary probably based on the Findings are similar to those found in Leigh syndrome or Wernicke encephalopathy, though the

widespread in the CNS. Poorly delineated necrotic lesions widely affect the pons, hypothalamus microscopically, these areas showed microcavitation, capillary proliferation, and gliosis. Myelinated neurons or axonal processes. Severe edema may be evident in many major white matter tracts

## TREATMENT

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### Medical Care:

- Therapy for biotinidase deficiency is oral biotin, typically administered as 10 mg/d.
- Some patients require higher dosages. If the enzymatic defect is present but does not respond to low-dose therapy (up to 40 mg/d).
- If children are left with residual neurological disease, they may require treatments for developmental dysfunction in addition to biotin.

### Consultations:

- An experienced child neurologist, metabolic specialist, or geneticist should assist in the evaluation and management of the child.
- A neurologist or a pediatrician skilled in the evaluation of a child who is neurologically impaired should perform the physical and neurological examinations and procedures to document residual neurological injury.



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- The Endocannabinoid System: The Mechanisms Behind Metabolic Homeostasis and Imbalance (Stephen C. Woods, PhD)
- Endocannabinoid Blockade for Improving Glycemic Control and Lipids in Patients With Type 2 Diabetes (Priscilla Hollander, MD, PhD)
- Panel Discussion (Moderator Louis J. Aronne, MD, FACP, with panelists Richard Bergman, PhD; Alan D. Cherrington, PhD; Robert R. Henry, MD; Priscilla Hollander, MD, PhD; and Stephen C. Woods, PhD)

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## MEDICATION

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**Drug Category:** *Vitamins and cofactors* -- Organic substances required by the body in sm processes. Used clinically for the prevention and treatment of specific deficiency states. Biotin

<b>Drug Name</b>	Biotin -- An essential coenzyme in fat metabolism and in other carboxylation reactions. Biotin deficiency may result in the urin excretion of organic acids and changes in skin and hair.
<b>Adult Dose</b>	10-40 mg/d PO
<b>Pediatric Dose</b>	6-40 mg/d PO
<b>Contraindications</b>	Documented hypersensitivity
<b>Interactions</b>	PO anticonvulsant medications may impair biotin absorption
<b>Pregnancy</b>	A - Safe in pregnancy
<b>Precautions</b>	None reported

## FOLLOW-UP

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### Complications:

- Failure to recognize and treat patients with biotinidase deficiency may lead to permanent audiological damage. Ultimately, death can occur.
- Immunological disruption may result in fulminant fungal infections.

### Prognosis:

- With treatment, patients have an excellent prognosis and potential for a normal lifestyle.

## MISCELLANEOUS

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### Medical/Legal Pitfalls:

- Due to the varied presentation in biotinidase deficiency and the potentially treatable natu unexplained seizures, encephalopathy, acidosis, optic atrophy, or paraparesis. Testing r
- Because parents subsequently may have a similarly affected child, genetic counseling n all children for the deficiency.

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