



# Multiple-CoA Carboxylase Deficiency

## Background

There are four carboxylase enzymes in man that require biotin for activity. These enzymes are propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, pyruvate carboxylase, and acetyl-CoA carboxylase. If biotin metabolism is defective, all four carboxylases will be deficient. Biotin is covalently linked to a key lysine residue in each carboxylase by action of holocarboxylase synthetase. When the carboxylase proteins are degraded, biotinoyl-lysine is subsequently cleaved by biotinidase releasing free biotin that can be reutilized. The two defects in biotin metabolism associated with Multiple Carboxylase Deficiency are caused by deficient activity of holocarboxylase synthetase and biotinidase. The disorders tend to present clinically at different ages, with holocarboxylase synthetase deficiency being known as early-onset (neonatal) multiple carboxylase deficiency and biotinidase deficiency referred to as late-onset multiple carboxylase deficiency. Both respond to biotin supplementation.

## Clinical

Patients affected with deficient holocarboxylase synthetase usually present in the first days or weeks of life with poor feeding, lethargy, hypotonia, and seizures, sometimes progressing to coma. Generalized rash and alopecia may be present. Affected patients exhibit metabolic acidosis and mild to moderate hyperammonemia. In contrast, Biotinidase deficiency, which constitutes the vast majority of patients with Multiple Carboxylase Deficiency, typically presents after several months of life with neurocutaneous symptoms including developmental delay, hypotonia, seizures, ataxia, hearing loss, alopecia, and skin rash. In some patients, the disease can be life-threatening.

## Testing

Biotinidase deficiency is readily detected by measuring the activity of the enzyme on a heel stick dried blood spot. Newborn screening using tandem mass spectrometry may reveal an elevation of C5-hydroxy acylcarnitine from the dried blood spot of a patient affected with holocarboxylase synthetase deficiency. Diagnosis of holocarboxylase synthetase deficiency requires further testing. Urine organic acid analysis reveals elevations of  $\beta$ -hydroxyisovaleric acid,  $\beta$ -methylcrotonylglycine, and tyglylglycine. Urine may also contain metabolites seen in Propionyl CoA Carboxylase deficiency and  $\beta$ -Methylcrotonyl CoA Carboxylase deficiency. Discriminating these disorders is important to ensure proper therapy is initiated.

## Treatment

Treatment of patients with Multiple Carboxylase Deficiency involves administration of high doses of biotin. An excellent and rapid clinical response to biotin is characteristic of both enzyme defects associated with Multiple Carboxylase Deficiency. This highlights the importance of accurate and timely diagnostic evaluation of affected infants.

Because the diagnosis and therapy of Multiple Carboxylase Deficiency is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician.

## Inheritance

This disorder most often follows an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

## References

Sweetman, L. and Williams, J.C. Branched Chain Organic Acidurias. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill.

Wolf, B. Disorders of Biotin Metabolism. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill.