

## 3-Methylglutaconyl-CoA Hydratase Deficiency

### Background

3-Methyl Glutaconyl-CoA Hydratase is an enzyme involved in the metabolism of the amino acid Leucine. It is located in mitochondria along with other associated enzymes of leucine catabolism. Deficiency of the enzyme leads to impaired leucine breakdown and massive excretion of 3-methylglutaconic acid. The gene has been cloned and some mutations identified in affected patients.

### Clinical

Few patients have been described with this disorder, but the disease seems to have a wide range of clinical severity. Some patients develop acute life-threatening cardiopulmonary symptoms soon after birth, whereas others have a more chronic picture with psychomotor retardation, hypotonia, failure to thrive, microcephaly, seizures, and spasticity. Some patients have acute episodes of vomiting, metabolic acidosis and lethargy progressing to coma. Carnitine levels are variably low. Recurrent acidosis is occasionally seen with prolonged fasting and/or intercurrent illness. Speech retardation was the isolated neurological manifestation in one family.

### Testing

Newborn screening for this disorder can be performed on a dried blood spot by tandem mass spectrometry. Infants with this disorder have increased C5-hydroxy acylcarnitine (C5-OH). This finding, however, is not specific to 3-Methyl Glutaconyl-CoA Hydratase Deficiency and the diagnosis requires additional testing. Urinary organic acid analysis reveals elevations of 3-methylglutaconate and 3-hydroxyisovalerate. The diagnosis can be confirmed with measurement of hydratase enzyme activity in lymphocytes or fibroblasts. Measurement of metabolites in amniotic fluid or enzyme assay of amniocytes may be useful for prenatal diagnosis. Knowledge of gene mutations in a family offers the potential for reliable prenatal diagnosis.

### Treatment

Treatment of 3-Methylglutaconyl-CoA Hydratase Deficiency involves reducing protein intake, particularly the branched-chain amino acid Leucine. Carnitine supplementation may be indicated. Prolonged fasting should be avoided, because it can exacerbate the abnormal biochemical findings.

Because the diagnosis and therapy of 3-Methylglutaconyl-CoA Hydratase 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

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