

# Hyperammonemia Hyperornithinemia Homocitrullinuria Syndrome (HHH)

## Background

Hyperornithinemia-Hyperammonemia-Homocitrullinuria (HHH) Syndrome was first described in 1969. In affected patients, plasma Ornithine is found to be dramatically elevated. Hyperammonemia is chronically present, but worsens postprandially. The etiology is a deficiency of a mitochondrial carrier protein that normally functions to transport Ornithine into the mitochondria as part of the urea cycle. When transport is defective, Ornithine accumulates in the cytosol and the urea cycle is impaired, resulting in hyperammonemia. The ORNT 1 gene that codes for the transport protein is located on chromosome 13, and several mutations have been identified in affected patients.

## Clinical

HHH Syndrome may present at birth, during childhood or even adulthood. Newborns who are breast fed usually have an uneventful beginning with intermittent hyper-ammonemia. Infants on high protein formula or foods may vomit with feeding, refuse to eat, become lethargic or develop hyperammonemic coma. Most affected patients exhibit some symptoms, such as lethargy, vomiting, ataxia or choreoathetosis, impaired growth and delayed development. Seizures are often reported. Mild to profound mental retardation is usually apparent by childhood. Over time, patients will gravitate to a diet low in milk and meat during childhood.

## Testing

Newborn screening of dried blood spots using tandem mass spectrometry (MS/MS) is capable of identifying and quantitating Ornithine. HHH Syndrome patients have Ornithine levels five to ten times normal. Alanine may be elevated. Hyperammonemia occurs postprandially and is chronically elevated on a high protein diet, but may be normal when fasting. Urine organic acid analysis will reveal elevated Orotic Acid while urine amino acid analysis finds elevated Homocitrulline, a metabolite of Ornithine. Elevated plasma Ornithine differentiates HHH Syndrome from other urea cycle defects. The disorder of Gyrate Atrophy of the Choroid and Retina, also with hyperornithinemia, is differentiated by its lack of hyperammonemia. Identification of mutations in the ORNT 1 gene allows for definitive diagnosis and carrier identification. Prenatal diagnosis is possible if the gene mutation has been identified in both parents.

## Treatment

Few patients with HHH Syndrome have been treated from an early age, prior to onset of disabling symptoms. Dietary restriction of protein is the basic treatment, with supporting therapy to prevent and control the hyperammonemia. A trial of Ornithine, Arginine, or Citrulline supplementation may reduce plasma ammonia. Patient response is highly variable.

Because the diagnosis and therapy of HHH Syndrome 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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