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Carbamoylphosphate Synthetase Deficiency

Background

Metabolism of amino acids generates ammonia, a highly toxic nitrogen-containing molecule that is eliminated from the body by its incorporation into urea, a non-toxic end product excreted through the kidneys. Carbamyl Phosphate Synthetase (CPS) catalyzes the first step in the detoxification of ammonia through formation of carbamyl phosphate, which enters the urea cycle and ultimately contributes its nitrogen to urea. Deficiency of CPS results in hyperammonemia and life-threatening symptoms. CPS is localized to the mitochondrial matrix and is present in high amount in liver and intestine. The CPS gene has been cloned and mutations identified in patients.

Clinical

Newborns with CPS deficiency appear normal for the first 24 hours. By 72 hours, symptoms of lethargy, vomiting, hypothermia, respiratory alkalosis and seizures progressing to coma appear. These patients are frequently thought to have sepsis. However, a key laboratory abnormality suggesting a urea cycle defect is low blood urea nitrogen, which should prompt measurement of ammonia. Patients who survive the newborn period often have recurrent episodes of hyperammonemia associated with viral infections or increased dietary protein intake. A neurologically damaged outcome is characteristic of CPS deficiency. Some patients have a later onset with a less severe course making diagnosis difficult.

Testing

Newborn screening by tandem mass spectrometry using a dried blood spot can detect elevated levels of glutamine and glutamate, together with low citrulline, suggesting CPS deficiency. Further testing is critical for the correct diagnosis. Plasma amino acids, urine organic acids and plasma acylcarnitine profiles will help distinguish CPS deficiency from other metabolic disorders exhibiting neonatal hyperammonemia. In contrast to several other urea cycle defects, patients with CPS deficiency do not excrete high levels of orotic acid. The activity of CPS can be measured in a liver biopsy. Mutation analysis of the CPS gene may be useful for prenatal diagnosis in future pregnancies.

Treatment

Treatment of acute hyperammonemia caused by CPS deficiency includes hemodialysis, peritoneal dialysis or arteriovenous hemofiltration. Several drugs conjugate major amino acids, forming metabolites that are excreted in the urine, which eliminates a major source of nitrogen from being converted to ammonia. Administration of sodium phenyl-butyrate (or phenylacetate) conjugates glutamine, forming phenylacetylglutamine, which is excreted by the kidneys and removes waste nitrogen. In a similar fashion, citrulline is given to conjugate aspartic acid forming argininosuccinic acid. Administration of sodium benzoate results in conjugation of glycine, which is subsequently excreted in the urine. Patients who survive the initial presentation are placed on chronic treatment with phenylbutyrate, benzoate and supplemental arginine along with dietary protein restriction. Patients having onset in the newborn period face a poor outcome and significant risk of neurological damage or demise.

Because the diagnosis and therapy of CPS deficiency is complex, the pediatrician is strongly 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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