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GENOMICS

5-Oxoprolinuria (Pyroglutamic Aciduria)

5-Oxoprolinemia – Glutathione Synthetase Deficiency
Glutamylcysteine Synthetase Deficiency
5-Oxoprolinase Deficiency

Background

5-Oxoprolinemia is a rare clinical condition caused by a deficiency of any one of three enzymes in the γ-Glutamyl Cycle. The Cycle provides antioxidant for the body in the form of Glutathione. Three enzymes are involved in the sequential processing of 5-Oxoproline to form glutathione. A deficiency of any one of the enzymes causes 5-Oxoprolinemia, and two of the defects lead to low levels of glutathione. Patients with 5-Oxoprolinemia have been described in several ethnic groups around the world.

Clinical

Clinical presentation of these deficiencies is variable, from severe to very mild. Gluta-thione Synthetase Deficiency is the most common defect, reported in over 40 cases worldwide. It usually presents in the newborn period with marked metabolic acidosis, hemolytic anemia, electrolyte imbalance, and jaundice. Patients who survive the initial onset may later have episodes of metabolic decompensation during intercurrent illnesses. They often develop progressive central nervous system symptoms. 5-Oxoproline can reach very high levels during illness.

Glutamylcysteine Synthetase Deficiency is less severe than Glutathione Synthetase Deficiency, lacking the metabolic acidosis and having lower 5-Oxoproline levels in plasma and urine. Patients have mild compensated hemolytic anemia as the most consistent finding.

Only a few patients have been reported with 5-Oxoprolinase Deficiency. Their clinical symptoms vary tremendously and may not be due to the metabolic defect. They have normal glutathione levels in erythrocytes and no evidence of hemolytic anemia.

Testing

Newborn Screening of dried blood spots using tandem mass spectrometry identifies 5-Oxoproline. Elevated levels should dictate further diagnostic testing. Glutathione Synthetase and Glutamylcysteine Synthetase activity can be measured in erythrocytes, leukocytes, and fibroblasts. 5-Oxoprolinase is not present in erythrocytes, but is present in leukocytes and fibroblasts. Glutathione Synthetase Deficiency has been diagnosed prenatally by enzyme assay of amniocytes or chorionic villi cells, or by finding elevated 5-Oxoproline in amniotic fluid. The gene is on chromosome 20 and mutations have been found in affected patients, raising the possibility for DNA-based prenatal diagnosis. Glutamylcysteine Synthetase is composed of two different proteins and mutations have been found in one of the genes.

Treatment

Patients with Glutathione Synthetase Deficiency require intravenous sodium bicarbonate for acute episodes and oral alkali for chronic acidosis. Severe anemia is corrected with blood transfusions. Patients with Glutathione Synthetase or Glutamylcysteine Synthetase Deficiencies may benefit from supplementation with Vitamin E and Vitamin C for their antioxidant effects.

Because the diagnosis and therapy of 5-Oxoprolinemia 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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