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Tyrosinemia

Background

Elevated blood Tyrosine levels are seen in three inherited disorders of Tyrosine metabolism. Tyrosinemia Type I was described in 1957 and is caused by deficiency of fumarylaceto-acetate hydrolase (FAH). While a predominance of patients are of French Canadian or Scandinavian decent, people from other ethnic groups have also been diagnosed. Tyrosinemia Type II, also known as Oculocutaneous Tyrosinemia, characteristically affects the cornea and skin, and is caused by deficiency of Tyrosine Aminotransferase, which acts at the first step in Tyrosine catabolism. Described in 1973, patients are predominately Italian, but other ethnic groups are represented as well. Tyrosinemia Type III is a rare disorder caused by deficiency of 4-hydroxyphenylpyruvate dioxygenase (4HPPD). Only a few patients have been described. In addition to the 3 inherited disorders, Transient Tyrosinemia of the Newborn is the major cause of tyrosine elevations detected on newborn screening.

Clinical

Tyrosinemia Type I usually presents in the first few months of life with progressive hepatorenal symptoms. Infants exhibit failure-to-thrive, hepatomegaly, liver dysfunction, together with metabolic acidosis and electrolyte disturbances due to renal tubular dysfunction (renal Fanconi syndrome). Diminished biosynthetic function of liver, which results in decreased clotting factors and a bleeding diathesis, often precedes large elevations in serum transaminases. Liver disease progresses to cirrhosis, hepatic failure, and death in undiagnosed patients. At any time, patients may develop acute hepatic crises with ascites, jaundice, and gastrointestinal bleeding. Neurologic episodes of painful paresthesias, weak-ness, paralysis, and respiratory insufficiency occur. There is a high risk for development of hepatic nodules and hepatocellular carcinoma. Most untreated patients die in infancy or early childhood. Patients with Type I disease do not have mental retardation.

Oculocutaneous Tyrosinemia (Type II) is associated with corneal ulcers and painful hyperkeratotic plaques on the palms and soles. Mental retardation may be present in a minority of patients. Symptoms are thought to arise from accumulation of Tyrosine that crystallizes in cells and tissues.

Patients with Tyrosinemia Type III develop neurologic problems, mental retardation and ataxia.

Transient Tyrosinemia of the Newborn is chiefly a self-limited metabolic condition often found in premature infants. The disorder is due to immaturity of 4HPPD enzyme activity in the liver. It usually resolves spontaneously by two months of age.

Testing

Tyrosine is readily measured in a newborn screening dried blood spot using tandem mass spectrometry. Mild to moderate elevations of Tyrosine that decrease and become normal with follow-up testing is consistent with Transient Tyrosinemia of the Newborn. This transient elevation is a pattern associated with liver immaturity or dysfunction.

Very high Tyrosine levels in the first screening specimen or high levels in a second specimen may point to an inherited metabolic defect. Workup of such patients includes measuring plasma amino acids and looking for succinylacetone on urine organic acid analysis. Elevations of plasma Tyrosine, often with methionine and perhaps a generalized aminoacidemia, are seen in Tyrosinemia Type I. The finding of succinylacetone in urine is pathognomonic for Type I disease. FAH activity is deficient in lymphocytes, erythrocytes, and liver tissue of Type I patients. Prenatal diagnosis for Type I can be accomplished by detecting succinylacetone in amniotic fluid and finding deficient FAH activity in chorionic villus cells or cultured amniocytes.

Patients with Tyrosinemia Type II usually have an isolated elevation of Tyrosine only. Tyrosine Aminotransferase (Type II) activity can be measured in liver and kidney.

Patients with Type III have 4-hydroxyphenylpyruvic and 4-hydroxyphenyllactic acids in their urine, which can be detected by organic acid analysis. 4HPPD enzyme activity is measured in liver.

The genes for both Type I and II Tyrosinemia have been cloned and mutations identified. Mutation analysis can be informative for family counseling and prenatal testing.

Treatment

Patients with Transient Tyrosinemia can benefit from reducing the protein level in formula and usually do well on breast milk. Normalization of the Tyrosine level is hastened by dietary supplementation with vitamin C. Patients with Type I disease must be treated aggressively with dietary restriction of Tyrosine and Phenylalanine, and administration of 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). This drug inhibits 4HPPD and lowers Tyrosine metabolites that are responsible for much of the Type I morbidity. Liver transplantation is a cure for patients with Type I disease, providing normal FAH activity. Patients with Type II Tyrosinemia also require dietary restriction of Tyrosine and Phenylalanine, respond to vitamin A supplementation in clearing of the skin lesions and should be given a trial of pyridoxine phosphate. Patients with Type III benefit from dietary Tyrosine and Phenylalanine restriction.

Because the diagnosis and therapy of Tyrosinemia 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

These disorders most often follow 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

Cerone, R., Holme, E., Schiaffino, M.C., et al. Tyrosinemia type III: Diagnosis and ten-year follow-up. Acta Pediatrics 86:1013, 1997.

Kvittingen, E.A., Rootwelt, H., Brandtzaeg, P., et al. Hereditary Tyrosinemia type I. J Clinical Investigation 91:1816, 1993.

Mitchell, G.A., Larochelle, J., Lambert, M., et al. Neurologic crises in hereditary Tyrosinemia. New England J Medicine 322:432, 1990.

Mitchell, G.A., Grompe, M., Lambert, M., Tanguay, R.M. Hypertyrosinemia. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill. Chapter 79, pg. 1777 -1805.

Sassa, S., Fujita, H. and Kappas, A. Succinylacetone and delta-aminolevulinic acid dehydratase in hereditary Tyrosinemia: Immunochemical study of the enzyme. J Pediatrics 86:84, 1990.

Shoemaker, L.R., Strife, C.F., Balistreri, W.F., and Ryckman, F.C. Rapid improvement in the renal tubular dysfunction associated with Tyrosinemia following hepatic replacement. J Pediatrics 89:251, 1992.