

Disease Name:

TYROSINEMIA, TYPE 1

HEPATORENAL TYROSINEMIA, FUMARYLACETOACETASE DEFICIENCY, FAH DEFICIENCY

Classification: Inborn Error of Amino Acid Metabolism

Genetic Information: **Inheritance:** Autosomal recessive

Population Incidence: 1:100,000

Ethnic Incidence: French Canadian

Gene & Location: 15q23-q25

Common Mutation: IVS12+5G-A (French Canadian 86% of alleles, 32% of alleles in U.S. & Europe) 20 known mutations.

OMIM # 276700

Disease Information: **Symptom Onset:** Prenatal liver disease. Severe forms present within a few weeks of birth. Chronic form presents later in infancy or childhood.

Symptoms: Severe form: Liver failure, vomiting, diarrhea, mild to moderate jaundice, hypoglycemia, ascites, bleeding diathesis, rickets and renal tubular dysfunction. Acute porphyria-like neurologic crises with abdominal pain, peripheral neuropathy, muscle weakness and hypertension occur periodically.
Chronic form: Asymptomatic to slight hepatomegaly, mild growth retardation and mild or sub-clinical rickets and renal tubular disease. Unfortunately, both forms lead to hepatocellular carcinoma that appears from infancy through adolescence.

Physical Findings: No dysmorphisms.

Treatment: Treatment is multi-pronged. Traditional treatment has been a low phenylalanine/tyrosine diet that is still used. In 1992 a new drug became available, 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione, thankfully known as NTBC (Nitisinone) that inhibits the degradation of tyrosine and the formation of toxic metabolites. Transplantation is done for non-responders to NTBC and for patients with suspected or proven carcinoma.

Natural History without treatment: See Severe and Chronic Symptoms above. Death in infancy from liver failure for the more severe forms and death in childhood or adolescence from liver carcinoma in milder forms.

**Natural History
with treatment:**

In 90% of patients dietary therapy and NTBC resolve the liver disease, clotting abnormalities, renal tubular disturbances and porphyria-like episodes. Growth and development remain normal. Unfortunately, it is not yet known if NTBC can prevent carcinoma. The only way to ensure protection from carcinoma is liver transplantation, which is itself not a benign procedure. Transplantation also “cures” tyrosinemia as donor enzyme is normal

**Metabolic
Information:**

**Missing Enzyme & Location:
MS/MS profile:**

Fumarylacetoacetase; widely distributed in tissues. Elevated tyrosine (120-1300 umol/l), methionine, galactose and phenylalanine may also be elevated if there is severe liver disease at the time of specimen collection. Measurement of tyrosine by MS/MS is nonspecific for tyrosinemias and patients may be missed.

Prenatal testing:

Chorionic villus, amniocentesis for succinylacetone in amniotic fluid. Assay of fumarylacetoacetase in Chorionic villus or amniocytes. There is a “pseudo gene” deficiency, where individuals have low enzyme activity upon testing, but are asymptomatic and do not have disease. The presence of this gene may confound prenatal results.

**Miscellaneous
Information:**

Diagnosis is confirmed by elevated succinylacetone or its metabolites in urine or plasma, absent fumarylacetoacetase activity in lymphocytes or fibroblasts or by DNA mutation analysis.

Prepared for the NW Regional Newborn Screening Program by Judi Tuerck, RN MS, Oregon Health & Science University

References:

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