TYROSINEMIA

Introduction

The tryrosinemias are a group of inherited disorders of amino acid metabolism, each caused by an enzymatic defect effecting tyrosine (TYR) catabolism, that leads to elevated levels of TYR. Tyrosinemia Type Ia is caused by a primary defect of hepatic fumarylacetoacetate hydrolyase (FAH) with production of an abnormal metabolite, succinylacetone, which is formed from the accumulated substrate fumarylacetoacetate. (See Figure 1)

Tyrosinemia Type I is an autosomal recessive condition. Heterozygotes are asymptomatic and have normal levels of tyrosine-related metabolites. The incidence is estimated to be 1 in 100,000 to 120,000 worldwide. Large numbers of cases have been reported in two regions, the Saguenay-Lac St-Jean region of Quebec, Canada and northern Europe, particularly Scandinavia and Finland, but lack of French-Canadian or Scandinavian ancestry does not exclude the diagnosis, since patients from a variety of ethnic backgrounds have been reported. FAH is expressed in amniotic and chorionic villus cells and prenatal diagnosis is available by biochemical or molecular techniques.

Tyrosinemia type Ib, an extremely rare condition, is believed to be due to deficiency of maleylacetoacetate isomerase and has only been reported in one patient. Liver failure, renal tubular disease, and progressive psychomotor retardation occurred prior to death at one year of age.

Tyrosinemia type II is an autosomal recessive condition characterized by greatly elevated concentrations of blood and urine tyrosine and by increases in urinary phenolic acids, N-acetyltirosine, and tyramine. Deficiency of hepatic cytosolic tryrosine aminotransferase (TAT) has been demonstrated. Characteristic physical findings include stellate corneal erosions and plaques and bullous lesions of the soles and palms. Persistent keratitis and hyperkeratosis occur on the fingers and palms of the hands and on the soles of the feet. These skin abnormalities respond to restriction of dietary phenylalanine and tyrosine. Intracellular crystallization of tyrosine is thought to cause these inflammatory responses. Mental retardation may occur.

Tyrosinemia type III is an autosomal recessive condition which results in dysfunction of p-hydroxyphenylpyruvic acid dioxygenase(p-OHPPAD) in the liver and kidney. Typically affected individuals suffer from neurological deficits and mental retardation. Dietary restriction of tyrosine and phenylalanine is required.
Clinical Features of Tyrosinemia type Ia

- Generalized renal tubular impairment with hypophosphatemic rickets.
- Progressive liver failure producing cirrhosis and hepatic cancer often in early childhood.
- Hypertension and edema.
- Episodic behavioral and peripheral nerve deficiencies.
- Elevated concentrations of blood phenylalanine (PHE) and TYR with succinylacetone and δ-ALA excretion in urine.
- Acute form of tyrosinemia type Ia—Soon after birth, infants develop progressive liver and kidney failure, vomiting, diarrhea, and a "cabbage-like" odor. Increased concentrations of phenylalanine, tyrosine and frequently methionine are found in the blood.
- The chronic form of tyrosinemia type Ia is similar to the acute form, but symptoms are usually milder and appear later in infancy. Symptoms include rickets, liver and kidney dysfunction, high blood pressure and nervous system dysfunction.

Diagnosis

Newborn screening—Tandem mass spectrometry identifies elevations in Tyrosine, Phenylalanine, and Methionine. An abnormal phenylalanine/tyrosine ratio may be present.

Confirmation—a second blood sample may be requested by the Newborn Screening Program and/or follow up testing will be done at a Metabolic Treatment Center. Elevated urinary succinylacetone; also look for elevated urinary 4-hydroxyphenylpyruvate, 4-hydroxyphenyllactate and d-ALA liver biopsy for assay of fumarylacetoacetase activity (though enzyme mosaicism may obscure the result).

Clinical Diagnosis—Tyrosinemia Type Ia should be suspected in any infant or child with evidence of hepatocellular lysis, cirrhosis, or decreased hepatic synthetic function (especially perturbed coagulation studies) for which the cause is not evident. The presence of hypophosphatemic rickets and other renal tubular diseases or of typical neurologic crises also suggests this diagnosis, especially if associated with abnormal hepatic function. Plasma tyrosine levels are initially elevated to a variable degree in almost all symptomatic patients. Older patients with a chronic course and patients treated with low-protein diets often have normal levels of plasma tyrosine.

Monitoring

- Support normal growth and development.
- Ultrasound/CT of the liver.
Serum Alpha fetoprotein levels

- Liver function tests, clotting studies, calcium, potassium and phosphate
- Blood tyrosine, phenylalanine, and methionine levels—maintain plasma and urine free (or trace) of succinylacetone and parahydroxyphenyl organic acids.

- It is also important for the primary care provider and the Metabolic Treatment Center to develop an on-going collaborative relationship in caring for patients with tyrosinemia.

Treatment

- Dietary restriction of tyrosine and phenylalanine. Aim to keep tyrosine level below 40-80µmol/l and phenylalanine 35-90µmol/l (as close to normal range as possible).
- Treatment with NTBC (2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione) to block metabolism prior to production of hepatotoxic fumarylacetoacetate.
- Liver transplantation when indicated. Renal transplant secondary to nephrocalcinosis may also be required.
- Injections of 1,25-hydroxyvitamin D may be required to heal rickets

Growth and development

As these patients are maintained on a restricted diet it is crucial to closely monitor all growth parameters on a regular basis. In cases with neurological deficits the child should be integrated into an early intervention program and developmental progress closely monitored by both the metabolic team and the primary care provider.
TYROSINE METABOLISM IN TYROSINEMIA TYPES 1A AND 1B.

Figure 1

Dietary protein

Phenylalanine*

Tissue protein synthesis

Melanin

Epinephrine

Thyroxine

Tissue protein catabolism

Tyrosine*

p-Hydroxyphenylpyruvic acid*

p-OH phenylpyruvic acid dioxygenase

Homogentisic acid

Maleylacetoacetic acid isomerase (type 1b)

Maleylacetoacetic acid*

Fumarylacetoacetic acid hydrolyase (type 1a)

Fumarylacetoacetic acid

Fumaric acid

Acetoacetic acid

*Succinylacetone

* Accumulates in untreated tyrosinemia type 1a

† Inhibited by NTBC

Enzyme malfunction
TYROSINE METABOLISM IN TYROSINEMIA TYPES II AND III

Figure 2