

TYROSINEMIA

There are 2 clinically recognized types of tyrosinemia. Type I (hepatorenal) tyrosinemia (OMIM database No. 276700)¹⁷⁶ is characterized by liver toxicity from increased concentrations of tyrosine and other metabolites with hepatocellular damage. Acutely, this produces jaundice and increased transaminase concentrations. Chronically, there is a high risk of hepatic cancer. Other features include the renal Fanconi syndrome and peripheral neuropathy.¹⁷⁷ Type I tyrosinemia is caused by deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). Type II (oculocutaneous tyrosinemia, also known as Richner-Hanhart syndrome; OMIM database No. 276600) exhibits corneal lesions and hyperkeratosis of the palms and soles. It is caused by deficiency of the enzyme tyrosine aminotransferase (TAT). A third entity, neonatal tyrosinemia, should be mentioned. It is more common in preterm infants and, in fact, is the most common cause of abnormal initial newborn screening results for tyrosinemia and PKU.¹⁷⁸ All show increased concentrations of serum tyrosine that can be detected on newborn screening.

Incidence

Type I tyrosinemia has an incidence of 1 in 12000 to 1 in 100000 in those of northern European descent. The incidence of type II and neonatal tyrosinemia has not been established.

Clinical Manifestations

Type I

Type I tyrosinemia in the acute form is characterized by failure to thrive, vomiting, diarrhea, a cabbage-like odor, hepatomegaly, fever, jaundice, edema, melena, and progressive liver disease. If untreated, death from liver failure may occur in the first year of life. The chronic form is similar but with milder features characterized by hypophosphatemic rickets. Other features have included hypertrophic obstructive cardiomyopathy, abdominal crises, polyneuropathy, hypertension, and hepatoma (a late complication in one third of patients). Death occurs during the first decade of life. There are increased concentrations of tyrosine in blood and urine. Urinary tests for succinylacetone and tissue analysis (liver or fibroblasts) for FAH activity establish the diagnosis.

Type II

Type II tyrosinemia is a distinctive oculocutaneous syndrome. Eye findings may be limited to lacrimation, photophobia, and redness. Signs may include mild corneal herpetiform erosions, dendritic ulcers, and, rarely, corneal and conjunctival plaques. Neovascularization may be prominent. Long-term effects include corneal scarring, nystagmus, and glaucoma. The skin lesions usually begin with or after the eye lesions. Skin findings may begin as painful, nonpruritic blisters or erosions that crust and become hyperkeratotic. They are usually limited to the palms and soles, especially the tips of the digits, and to the thenar and hypothenar eminences. They may be linear or subungual. A skin biopsy is not diagnostic and may show nonspecific hyperkeratosis, acanthosis, and parakeratosis. Skin lesions may be difficult to distinguish from any of the more common forms of keratosis. Mental retardation is an inconstant feature; mild-to-moderate retardation, self-mutilating behavior, disturbances of fine motor coordination, and language deficits have been reported. Tyrosinemia is the diagnostic feature of this disorder. Tyrosine is the only amino acid that is found in increased concentrations in the urine in this disorder.

Neonatal

Clinical findings in neonatal tyrosinemia are nonspecific. Infants with persistent neonatal tyrosinemia may be somewhat lethargic and have difficulty swallowing, impaired motor activity, prolonged jaundice, and increased levels of galactose, phenylalanine, histidine, and cholesterol. Mild acidosis may be present in approximately half of the infants. Mild retardation and decreased psycholinguistic abilities have been noted in some studies.¹⁷⁹

Pathophysiology

Type I

This disorder, although not a primary disorder of tyrosine metabolism, is accompanied by increased concentrations of tyrosine and its metabolites, which inhibit many transport functions and enzymatic activities. It has been proposed that the degree of residual FAH activity determines whether the disease will be acute or chronic in the affected patient.

Type II

This disorder is associated with a deficiency of hepatic TAT, the rate-limiting enzyme of tyrosine catabolism. Tyrosinemia, tyrosinuria, and increases in urinary phenolic acids, *N*-acetyltyrosine, and tyramine persist for life. The metabolism of other amino acids and renal and hepatic function are otherwise normal.

Neonatal

It is generally assumed that this disorder is caused by a relative deficiency of *p*-hydroxyphenylpyruvate oxidase stressed by high-protein diets, with resulting high tyrosine and phenylalanine concentrations. Others have suggested a mild decrease in TAT activity.

Inheritance

Type I and II tyrosinemias are autosomal recessive, with a 25% risk of recurrence in siblings. The heterozygotes for type I have approximately half-normal levels of FAH activity in fibroblasts and lymphocytes. Prenatal diagnosis is complex, requiring at least 3 different procedures using amniotic fluid and cultured amniocytes or chorionic villus cells. These procedures involve the direct measurement of succinylacetone by combined gas chromatography and mass spectrometry in amniotic fluid, FAH enzymatic activity, and the measurement of the ability of succinylacetone to inhibit aminolevulinic dehydrase activity in cultured amniotic fluid or chorionic villus cells.¹⁸⁰

The carrier state for type II tyrosinemia has not been detected biochemically, and prenatal diagnosis is not currently available. The inheritance of neonatal tyrosinemia is unclear.

The chromosome map location for type I (FAH) is 15q23-25, the location for type II (TAT) is 16q22.1–22.3, and the location for neonatal (*p*-hydroxyphenylpyruvate) oxidase is 12q24-qter. Type I tyrosinemia is most prevalent in French Canadians, with an overall incidence of as high as 1 in 700 in certain regions of Quebec.¹⁸¹ Type II tyrosinemia cases have been described in several countries including the United States, Canada, Japan, Europe, and the Middle East. Neonatal tyrosinemia is most prevalent in Canadian Inuits.

Rationale for and Benefits of Newborn Screening\

Death from complicating liver failure occurs in untreated patients with type I tyrosinemia during the first year of life in the acute form and during the first decade of life in the chronic form. Hepatocellular carcinoma may also be a cause of death. The introduction of 2-(2-nitro-4-trifluoromethylbenzyl)-1,3-cyclohexanedione (NTBC) has changed the outcome of this disorder dramatically.¹⁸² More than 90% of patients respond clinically to treatment with NTBC. The current indications for liver transplantation in type I tyrosinemia are nonresponsiveness to NTBC, risk of malignancy, and decreased quality of life related to dietary restriction and frequency of blood sampling. Successful liver transplantation can further reduce the mortality rate in nonresponders to 5%.¹⁸³ There is a strong decrease in the risk of early development of hepatocellular carcinoma in patients with effective, early therapy.

Screening

The BIA can be used to screen for tyrosinemia using dried blood spots. Abnormal concentrations of tyrosine are reported as more than 6 mg/dL. Newer methods include direct measurement of tyrosine by MS/MS. The test is performed in the neonatal period, but the optimal time for study is unclear. Presumably, it is best if measurements are obtained 48 to 72 hours after milk feeding. The stability of tyrosine in specimens has not been determined specifically but should be similar to that of phenylalanine. The rate of false-negative results has not been determined. Data from the 1999 National Newborn Screening Report¹⁸⁴ showed an initial positive screening result in 136 of 407118 newborn infants tested (1 in 3000), with 2 positive confirmed cases. Available data on second screenings performed between 1 and 4 weeks of age showed 2 positive results in 60474 infants (1 in 30000); no cases of tyrosinemia were confirmed among this group.

Follow-up and Diagnostic Testing

An increased tyrosine concentration on newborn screening requires confirmation and additional testing, because it may be caused by other metabolic disorders (eg, fructose and galactose enzyme deficiencies), giant cell hepatitis, neonatal hemochromatosis, and neonatal infections. The optimal approach is complex and requires determination of the concentrations of tyrosine and other amino acids and metabolites in the blood and urine. Type I tyrosinemia involves increased concentrations of urine succinylacetone and nonspecific aminoaciduria and requires tissue analysis (fibroblasts, erythrocytes, lymphocytes, or liver) for FAH activity. Type II tyrosinemia involves increased tyrosine concentrations only in blood and urine. Confirmation of neonatal tyrosinemia depends on the presence of increased concentrations of tyrosine and phenylalanine.

Brief Overview of Disease Management

Type 1

Treatment options for tyrosinemia include dietary therapy, liver transplantation, and use of the pharmacologic agent NTBC. Clinical signs and symptoms improve with NTBC therapy and diet.¹⁸² Signs of improvement include a decrease in concentrations of metabolites, correction of the secondary abnormality in porphyrin synthesis, improved liver and renal tubular function, and regression of hepatic abnormalities by computed tomography. Correction of porphyrin synthesis reduces the risk of porphyric crises.

Type II

Therapy with a diet low in tyrosine and phenylalanine is curative in type II tyrosinemia. Early diagnosis can help avoid the risk of mental retardation in these patients.

Neonatal

Most cases of neonatal tyrosinemia, especially those seen in small preterm infants, may be transient and controlled by reducing the protein intake to 2 to 3 g/kg per day or by breastfeeding. Some patients respond to ascorbic acid supplementation.

Current Controversies

The incidence and pathogenetic mechanisms of specific disorders associated with increased concentrations of tyrosine require clarification. The consequences of early diagnosis and treatment for type I tyrosinemia (the most formidable disorder in this group) should be beneficial. NBTC therapy seems to be very effective. No marked adverse effects have been noted. Follow-up for long-term outcome is needed.

Special Issues/Concerns

Confirmation of the exact cause of increased concentrations of tyrosine requires referral and evaluation by an expert in the field. Outcome with treatment remains variable.

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