

Current management options for tyrosinemia

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Abstract: Hypertyrosinemia is observed in three inherited disorders of tyrosine metabolism. Hereditary Tyrosinemia Type I (HTT-I), or hepatorenal tyrosinemia, is an autosomal recessive disorder caused by mutation in the fumarylacetoacetate hydrolase (*FAH*) gene. HTT-I is associated with severe involvement of the liver, kidneys, and central nervous system, and is due to toxic accumulation of metabolites of tyrosine, such as succinylacetone. HTT-I is the inborn error with the highest incidence of progression to hepatocellular carcinoma. Elevated succinylacetone, in dried filter paper blood samples, or in plasma or urine, is pathognomonic and diagnostic for HTT-I and is the most reliable neonatal screening method. Liver transplantation is the definitive management, but the need for this is markedly decreased by the combined dietary and drug management. A diet low in tyrosine and phenylalanine, plus nitisinone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione) (NCTB) are considered the gold standard management options. Carnitine and 1,25-OH-vitamin D are adjuvant therapy. Strict follow up with succinylacetone level for monitoring of treatment should be done. Abdominal ultrasonography and abdominal computerized tomography scan or magnetic resonance imaging should also be done for surveillance of the possible development of hepatocellular carcinoma.

Keywords: tyrosinemia, management, NTBC, hepatocellular carcinoma

Introduction and background

Tyrosine is obtained from ingested proteins and is synthesized endogenously in humans from phenylalanine. It is used for protein synthesis and is a precursor of dopamine, norepinephrine, epinephrine, melanin, and thyroxin. Hypertyrosinemia is observed in three inherited disorders of tyrosine metabolism.¹ Hereditary Tyrosinemia Type I (HTT-I; MIM 276700) is an autosomal recessive disorder caused by homozygous or compound heterozygous mutation in the encoding fumarylacetoacetate hydrolase (*FAH*) gene, encoding *FAH*, on chromosome 15q23-q25.² More than 40 mutations have been reported.³⁻⁴ The first report of a patient with elevated blood tyrosine was by Medes, in 1932.⁵ Patients with a more typical clinical and biochemical picture of tyrosinemia were then described in the late 1950s.⁶⁻⁹ Since then, more than 500 patients have been reported in the literature.¹⁰⁻¹² While a predominance of patients are of French Canadian or Scandinavian descent, people from other ethnic groups have also been diagnosed.¹³ Hereditary Tyrosinemia Type II (HTT-II) is a rare autosomal recessive disorder caused by deficiency of tyrosine aminotransferase, which acts at the first step in tyrosine catabolism.¹⁴ Described in 1973, patients are predominately Italian, but other ethnic groups are represented as well.¹³ Hereditary Tyrosinemia Type III

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(1) an active phase of acute peripheral neuropathy²⁸ with severe pain, often in the legs, associated with hypertonia (causing hyperextension of the trunk and neck), vomiting, paralytic ileus, and occasionally, self-induced injuries;^{23,30} (2) a period of recuperation, with marked weakness and paralysis occurring in about 30% of episodes, which may lead to respiratory failure and death.^{17,23} These crises may last one to seven days.²³

Renal involvement is manifested as a Fanconi-like syndrome with a normal anion gap metabolic acidosis, hyperphosphaturia, hypophosphatemia, glucosuria, aminoaciduria,^{1,10,14} and vitamin D-resistant rickets.³¹ Nephromegaly^{10,32} and some degree of nephrocalcinosis are often found.²³ Chronic renal failure may occur in adolescents and young adults.^{33,34}

Hypertrophic cardiomyopathy is occasionally seen in these infants.^{35–37} Edwards et al³⁸ described an obstructive cardiomyopathy in two symptomatic cases.

Hyperplasia and hypertrophy of the islets of Langerhans have been reported in a large number of cases,^{10,39–40} and hyperinsulinism has occasionally been documented.⁴¹

Chronic hypoglycemia has rarely been documented, and most patients have normal blood glucose levels.²³ Patients with HTT-I do not have mental retardation.¹⁴

HTT-II (Richner-Hanhart Syndrome or oculocutaneous tyrosinemia)

This disorder results in accumulation of tyrosine that crystallizes in cells and tissues, leading to palmar and plantar punctate hyperkeratosis, herpetiform corneal ulcers, and mental retardation.⁴² The eye manifestations of excessive tearing, redness, pain, and photophobia may occur before skin lesions. Corneal lesions usually occur during the first few months of life. Skin lesions, which may develop later in life, include painful, nonpruritic hyperkeratotic plaques on the soles, palms (especially thenar and hypothenar areas), and finger tips.⁴³ Mental retardation, which occurs in less than 50% of patients, is usually mild to moderate and may be associated with self-mutilation.⁴² Hepatic and renal functions remain intact.²³

HTT-III

Only four cases with this disorder have been reported.¹ They all have various neurologic findings but no consistent clinical phenotype.⁴² Age at onset has been from one–17 months.¹

Developmental delay, seizures, intermittent ataxia, and self-destructive behavior have been the main neurologic

findings. No liver or renal abnormalities are present. The first affected individual came to medical attention because of mental retardation and ataxia; another was detected on routine screening.⁴⁴

These individuals, like those with HTT-II, have no liver involvement but have skin and/or ocular changes. It remains unclear whether HTT-III is truly associated with cognitive delays or whether the association has resulted from ascertainment bias.⁴⁵

Transient tyrosinemia of the newborn

In a small number of newborn infants, plasma tyrosine may rise to as high as 60 mg/dL during the first two weeks of life.¹ Most affected infants are premature and receiving high-protein diets. The condition resolves spontaneously and is presumed to be due to delayed maturation of 4-HPPD in the liver.¹⁴ Lethargy, poor feeding, and decreased motor activity occur in some of these infants, but most are asymptomatic and come to medical attention because of a high blood phenylalanine level detected by the screening test for phenylketonuria.²³

Investigations

HTT-I

HTT-I is diagnosed from abnormalities found in biochemical investigations, imaging studies, liver biopsy, enzyme assay, genetic testing and mutation analysis, prenatal screening, and neonatal screening, as follows.

Biochemical investigations

a. Basic investigations

- Complete blood count: normocytic anemia¹
- Liver function tests: elevation of serum unconjugated and conjugated bilirubin, transaminases, and gamma glutamyl transpeptidase with hyperammonemia and marked compromise in hepatic synthetic functions, with hypoprothrombinemia^{1,17,46}
- Kidney function tests: picture of Fanconi Syndrome with hypophosphatemia, hyperphosphaturia, glucosuria, aminoaciduria, metabolic acidosis.^{1,17,46} Blood urea nitrogen and creatinine may be elevated⁴⁷
- Blood biochemistry: hypoglycemia^{17,46}
- Bone biochemistry: high alkaline phosphatase (rickets).⁴⁷

b. Specific investigations

- Serum and cord blood α -fetoprotein: marked elevation^{1,17,46}

- Serum amino acids: moderate increase of tyrosine ($>300 \mu\text{mol/L}$), phenylalanine, and other amino acids, especially methionine (secondary inhibition of methionine adenosyltransferase)^{1,17,22,46}
- Urinary amino acids: generalized hyperaminoaciduria⁴⁶
- Urinary delta-ALA: increased^{1,46}
- Elevated succinylacetone in blood or urine is pathognomonic and diagnostic.^{46,48–51}

Imaging studies

- Abdominal ultrasonography, computed tomography, or magnetic resonance imaging (MRI):⁵² heterogeneous liver parenchyma, hypoechogenic hepatic micronodules ($<5 \text{ mm}$), and hyper- or hypoechogenic macronodules ($\geq 5 \text{ mm}$). There may be nephromegaly +/- nephrocalcinosis.^{23,46} MRI with contrast can differentiate regenerative nodules from those of HCC, as the former contain functioning hepatocytes, which can uptake the contrast and excrete it in bile, while the latter don't and thus show reduced enhancement.²³
- X ray of the wrist: for evidence of rickets.^{47,53}

Liver biopsy

- Compatible with chronic hepatitis and nonspecific cirrhosis,¹ with pseudo acinar formation.¹⁷

Enzyme assay

- FAH activity in lymphocytes,⁵⁴ erythrocytes,⁵⁵ fibroblasts, and liver biopsy specimens;²³ the degree of residual enzyme activity dictates the disease severity.^{13,46}

Genetic testing and mutation analysis

- Many mutations in the *FAH* gene have been described.⁴⁴ The IVS12+5ga allele accounts for about 90% of mutant *FAH* alleles in the Saguenay–Lac St-Jean area of Quebec.^{56,57} IVS12+5ga and IVS6–1gt are frequent in patients of diverse ethnic origins.⁵⁸ In addition, W262X is prevalent in Finns,^{59,60} and Q64H (192GT) in Pakistanis.⁶¹ R341W causes pseudodeficiency.⁶²

Prenatal diagnosis

- 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.^{13,46}

Neonatal screening

- Measurement of succinylacetone in a dried blood spot, using tandem mass spectrometry:^{46,49,50,63–65} Screening using blood tyrosine as a marker leads to many false-positive results, in newborns with transient tyrosinemia, in those with other hereditary tyrosinemias, and occasionally in children with hepatic problems other than hepatorenal tyrosinemia;²³ more importantly, false-negative results may be obtained in children affected with hepatorenal tyrosinemia,⁴⁴ particularly in this era of low neonatal protein intake (breast-feeding, humanized formulas) and early hospital discharge, two factors that reduce the levels of blood tyrosine in predischARGE samples.²³

This condition should be differentiated from other causes of hepatitis and hepatic failure in infants, including galactosemia, hereditary fructose intolerance, neonatal iron storage disease, biliary atresia, and severe neonatal giant-cell hepatitis.^{1,46}

HTT-II

Abnormal laboratory findings include the following: (1) significant isolated hypertyrosinemia, typically $>500 \mu\text{mol/L}$ and may exceed $1000 \mu\text{mol/L}$, and tyrosinuria.⁵³ (2) Increased excretion of p-hydroxyphenylpyruvate, p-hydroxyphenyllactate, and p-hydroxyphenylacetate, and the presence of small quantities of N-acetyl tyrosine and 4-tyramine on urine organic acid analysis.⁵³ In contrast to HTT-I, liver and kidney functions, as well as serum concentrations of other amino acids, are all normal.¹

Tyrosine aminotransferase activity can be measured in the liver and kidneys.¹²

HTT-III

The diagnosis is established by moderate increases in plasma levels of tyrosine ($350\text{--}700 \mu\text{mol/L}$), the presence of 4-hydroxyphenylpyruvic acid and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids) in urine, and low activity of 4-HPPD enzyme in liver biopsy.^{1,13}

Transient tyrosinemia of the newborn

Laboratory findings include marked elevation of plasma tyrosine with a moderate increase in plasma phenylalanine. The presence of marked hypertyrosinemia differentiates this condition from phenylketonuria. As well, 4-hydroxyphenylpyruvic acid and its metabolites (4-hydroxyphenyllactic and 4-hydroxyphenylacetic acids) are also present in the urine.¹

Treatment

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 and a dietitian. It is recommended that parents move with a letter of treatment guidelines from the patient's physician.¹³

HTT-I

Previously, almost all patients died in infancy and early childhood. In the 50 years since the description of tyrosinemia,⁷ the course of the disease has been improved successively by the introduction of diet therapy, neonatal screening, and hepatic transplantation. The advent of liver and kidney transplantation as a definitive treatment revolutionized the outcome.^{11,12,66–68} Recently, the availability of nitisinone (NTCB), a peroral inhibitor of the tyrosine catabolic pathway (at an early step preceding the metabolic defect),^{69,70} has provided hope for a nonsurgical solution.

Management of HTT-I includes: (a) adequate supportive management for hepatic and neurologic crises and renal effects (which now rarely occur with combined dietary and NTCB management);^{1,53} (b) drug management; (c) dietary management; (d) liver transplantation; (e) gene therapy and hepatocyte transplantation; (f) genetic counseling; and (g) cognitive evaluation.

Drug management

Primary drug management

NTCB, 2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione (Orfadin[®], Swedish Orphan Biovitrum, Stockholm, Sweden), is the mainstay of treatment of HTT-I.⁷¹

NTBC is a triketone with herbicidal activity that has been shown to have a novel mode of action – by inhibiting the enzyme 4-HPPD in plants.⁷¹ Inhibition of 4-HPPD, the second step in the tyrosine degradation pathway, prevents the formation of tyrosine toxic metabolites.¹⁹ In 1991, Lindstedt et al⁷⁰ discovered the potential of NTBC in the treatment of HTT-I, and they successfully used it in five patients. This report led to widespread clinical trials that largely reproduced the original experience.¹⁷ Its efficacy in the treatment of HTT-I has well been recognized, and it was approved by the United States Food and Drug Administration (FDA) in April 2002.⁷² NTBC has radically improved the course of the disease, preventing acute hepatic and neurologic crises. It has improved the survival and quality of life of patients.^{18,73–78}

The recommended starting dose of NTBC is 1 mg/kg/day, divided into two daily doses (Orfadin European Public Assessment Report [EPAR] product information, Orfadin package insert).^{19,79} Recently, it has been reported that doses lower than 1 mg/kg/day have also been effective in the treatment of HTT-I.^{80,81} Based on the fact that the half-life of NTBC is known to be 54 hours,⁸² Schlune et al,¹⁹ used a single daily dose regimen in their patients, and they suggested that a single daily dose is as effective as the two daily doses and that it improves adherence.

NTBC can be quantified in plasma and blood spots to identify the optimal required dose.^{83,84} Dosage should be adjusted to maintain blood NTBC levels between 40 and 60 $\mu\text{mol/L}$, which, theoretically, blocks greater than 99% of 4-HPPD activity.⁵³ Rarely, an individual may require higher blood levels of NTBC (70 $\mu\text{mol/L}$) to suppress succinylacetone excretion.⁵³ Sander et al, reported a patient in whom a plasma NTBC concentration of 17 $\mu\text{mol/L}$ was effective.⁸⁴

NTBC should be taken on an empty stomach at least 1 hour before a meal. For children who are unable to swallow capsules, the capsules may be opened and the contents mixed in a small amount of water, formula, or apple sauce immediately before use.⁸⁵

Although NTBC stops or greatly slows disease progression, any pretreatment advanced liver damage is irreversible. Therefore, patients must be closely followed for development of HCC.

NTBC is effective but very expensive.⁸⁶ It is well tolerated, with few reported side effects,^{75–77} including transient low platelet and neutrophil counts, which may resolve without intervention and photophobia, which resolves with stricter dietary control and subsequent lowering of blood tyrosine concentrations.⁵³ It has been found that 4-HPPD inhibition tends to raise plasma tyrosine concentration, which may be responsible for the neurotransmitter changes recently documented by Thimm et al.⁸⁷

Other drug management options

Other drug management options include carnitine supplementation and 1,25-OH-vitamin D.

Carnitine deficiency can occur secondarily to renal tubular Fanconi Syndrome, causing skeletal muscle weakness. The serum concentration of carnitine should be measured so that carnitine deficiency, if identified, can be treated.⁸⁸

Osteoporosis and rickets, resulting from renal tubular damage, are treated by the correction of acidosis, restoring calcium and phosphate balance, and the administration of 25-OH-vitamin D.⁵³

Dietary management

A diet low in phenylalanine and tyrosine may result in some clinical improvement in some patients. However, the progression of the disease cannot be halted by diet alone,⁷³ with average age of survival less than ten years.¹ NTCB increases blood concentration of tyrosine, necessitating a low-tyrosine diet to prevent tyrosine crystals from forming in the cornea. Dietary management should be started immediately upon diagnosis and should provide a nutritionally complete diet with controlled intakes of phenylalanine and tyrosine, using a vegetarian diet with low-protein foods and a medical formula such as Tyrex® (Ross) or Tyros® (Mead Johnson). Phenylalanine and tyrosine requirements are interdependent and vary from individual to individual and within the same individual depending on growth rate, adequacy of energy and protein intakes, and state of health. With appropriate dietary management, plasma tyrosine concentration should be maintained at 200–500 µmol/L, regardless of age, and plasma phenylalanine concentration should be 20–80 µmol/L. If the blood concentration of phenylalanine is too low (<20 µmol/L), additional phenylalanine should be added to the diet, from milk or foods.⁵³

Liver transplantation

Prior to the availability of NTCB, liver transplantation was the only definitive therapy for the treatment of HTT-I, but now, this should be reserved for those children who: (1) have severe liver failure at clinical presentation and fail to respond to NTCB therapy; or (2) have documented evidence of malignant changes in hepatic tissue.⁸⁹ In some countries, liver transplantation is considered in patients with good response to NTCB due to financial issues, attributed to the very high cost of NTCB.⁸⁶ Whether treatment with NTCB alleviates or delays the need for liver transplantation remains to be determined.¹ Although the new liver will not produce succinylacetone, the kidneys still may do;⁴⁶ therefore, transplant recipients may benefit from low-dose NTCB therapy to prevent continued renal tubular and glomerular dysfunction resulting from the succinylacetone generated in renal tissue.⁹⁰

Gene therapy and hepatocyte transplantation

Although gene therapy and hepatocyte transplantation currently are not treatment options, they have received considerable publicity and are producing interesting results in mice.^{91–94}

Gene replacement therapy is theoretically more difficult in tyrosinemia than in certain other inborn errors of metabolism because the toxic intermediates in tyrosinemia are felt to be capable of inducing HCC, and possibly kidney disease,

even in the presence of normal circulating tyrosine levels; therefore, for treatment of tyrosinemia, it would not suffice to simply produce a sufficient number of cells to normalize plasma tyrosine – all hepatocytes would have to express normal FAH to avoid the risk of progression to cancer.²³

Biologically, cells with a functional *FAH* gene would have a selective advantage and might overgrow FAH-deficient cells, especially in mice.^{91–94}

At a clinical level, it is not clear how nodules that would arise from this process could be reliably distinguished from neoplastic nodules. If major improvements occur in gene transfer technology, in vivo cell selection, and the detection of hepatocellular carcinoma, they could have an important impact on the feasibility of gene therapy or hepatocyte transplantation in tyrosinemia.²³

Genetic counseling

As with all genetic diseases, genetic counseling is appropriate to help families understand the recurrence risks and ensure that they receive proper evaluation and care.¹³

Cognitive evaluation

Cognitive evaluation,⁷⁷ by a developmental psychologist, should be done close to school age and then at around age 10, to see how the patient is intellectually developing. About 35% of patients with HTT-I appear to have significant learning difficulties; the etiology of these cognitive defects is uncertain.⁴⁶ Patients with tyrosinemia who are treated appropriately will have the same intellectual potential as their siblings without tyrosinemia.⁴⁶

Monitoring of combined dietary and NTCB management

With adequate treatment, complete blood count indices, liver and kidney function tests normalize, α -fetoprotein levels drop rapidly until normalized, and succinylacetone disappears from the blood (<0.1 µmol/L) and urine (<1 µmol/mol creatinine).⁴⁶ Delta-aminolevulinic acid urine levels should be between 0–3 µmol/mol creatinine.²⁰

Tyrosine, phenylalanine and methionine should be measured to ensure that dietary management is appropriate for the patient's weight and size. Blood tyrosine levels should be maintained between 200 and 500 µmol/L, as higher levels can lead to tyrosine crystals in the eyes. Blood phenylalanine levels should be between 35 and 120 µmol/L.⁴⁶

NTCB blood levels should be maintained between 30–60 µmol/L. These should be done in the first six months following initiation of treatment, then every three to six months thereafter.^{46,53} Abdominal ultrasonography

should be done every six months forever and abdominal computerized tomography scan or magnetic resonance imaging annually.⁴⁶

HTT-II

In HTT-II, a diet low in tyrosine and phenylalanine corrects the chemical abnormalities and results in dramatic healing of the skin and eye lesions.⁴⁵ It is necessary to achieve a total intake of phenylalanine and tyrosine < 100 mg/kg/day to obtain plasma concentrations of tyrosine < 10 mg/dL.⁹⁵

Patients respond to vitamin A supplementation with clearing of the skin lesions, and they should also be given a trial of pyridoxine phosphate. Mental retardation may be prevented by early dietary restriction of tyrosine.¹³

HTT-III

A diet low in tyrosine and phenylalanine in combination with vitamin C supplementation causes a dramatic decrease in plasma tyrosine levels.^{13,45}

Transient tyrosinemia of the newborn

Here, hypertyrosinemia usually resolves spontaneously during the first month of life. It is often corrected promptly by reducing the amount of protein in the diet to 2 g/kg/24 hr and the infant usually does well on breast milk. Normalization of tyrosine level is hastened by vitamin C supplementation (200–400 mg/24 hr).^{1,13}

Disclosure

The authors report no conflicts of interest in this work.

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