Tyrosinemias

Contents

The genetic tyrosinemias, autosomal recessive disorders, are characterized by the accumulation of tyrosine in body fluids and tissues. There are three types of tyrosinemias: Types I, II, and III. Type I has a prevalence of about 1 in 100,000 newborns in the general population. Type III is extremely rare (Fig. 1).

Synonyms and Related Disorders

Congenital tyrosinosis; Fumarylacetoacetate hydrolase deficiency; Hawkinsinuria; Hepatorenal tyrosinemia; Hereditary tyrosinemia; Tyrosinemia, Type I; Tyrosinemia, Type II (oculocutaneous tyrosinemia, keratosis palmoplantaris with corneal dystrophy, Richner-Hanhart syndrome); Tyrosinemia, Type III

Genetics/Basic Defects

1. Tyrosinemia, Type I (Scott 2006)
    1. Caused by a deficiency of fumarylacetoacetate hydrolase (FAH) (Lindblad et al. 1977)
    2. Coded by the gene localized at 15q23-q25
2. Tyrosinemia, Type II
    1. Caused by a deficiency of tyrosine aminotransferase (TAT) (Goldsmith et al. 1973)
    2. Coded by the gene localized at 16q22
    3. More common in Italy where a common mutation (R57X) has been identified (Huhn et al. 1998)
3. Tyrosinemia, Type III
    1. Caused by a deficiency of 4-hydroxyphenylpyruvic dioxygenase (4-HPPD).
    2. Coded by the gene localized at 12q24-qter.
    3. A single mutation, A33T, is common in each of the families in which Hawkinsinuria has been identified (Tomoeda et al. 2000). Hawkinsinuria is somewhat unique in that it is inherited as an autosomal dominant, while other mutations of 4-HPPD cause the autosomal recessive tyrosinemia, Type III.

H. Chen, *Atlas of Genetic Diagnosis and Counseling*,
DOI 10.1007/978-1-4939-2401-1_279

Clinical Features

1. Tyrosinemia, Type I (Scott 2006; de Laet et al. 2013)
    1. Onset of disease
        1. Onset before 6 months of age: acute severe liver involvement
        2. Onset after 6 months of age (van Spronsen et al. 1994):
            1. Mild liver dysfunction
            2. Renal involvement
            3. Growth failure
            4. Rickets
    2. Hepatic disease
        1. Acute severe liver involvement: common with clotting abnormalities, ascites, and edema secondary to hypoalbuminemia
        2. Frequent hemorrhage
        3. Usually mild jaundice
        4. Firm and hard liver on physical examination
        5. Go on to develop cirrhosis, liver nodules, and hepatocellular carcinoma
    3. Renal disease
        1. Characteristic finding: tubular disorder with a Fanconi syndrome, the severity of which is variable.
        2. Typical features: aminoaciduria, glycosuria, phosphaturia, and renal tubular acidosis.
        3. Hypophosphataemic rickets.
        4. May progress to nephrocalcinosis, glomerulosclerosis, and chronic renal failure.
        5. Although renal disease may be the predominant feature, there is always some coexisting liver disease of varying severity.
    4. Neurologic disease
        1. Porphyria-like syndrome: most characteristic, usually precipitated by intercurrent infection
        2. Crises
            1. Pain can be severe including abdominal pain mimicking an acute surgical emergency.
            2. Weakness.
            3. Autonomic changes such as hypertension.
            4. Acute progressive ascending motor neuropathy, often with respiratory distress requiring assisted ventilation.
2. Tyrosinemia, Type II
    1. Ocular symptoms
        1. Onset: during first year of life.
        2. Recalcitrant pseudodendritic keratitis with photophobia, scleral inflammation, and pain (Macsai et al. 2001).
        3. Some degree of corneal ulceration and occasional birefringent crystals of tyrosine may be observed by slit lamp examinations.
    2. Skin lesions
        1. Hyperkeratotic plaques on the soles of the feet and palms of the hands.
        2. Dramatic yellowish thickening associated with the hyperkeratosis may be seen in the plantar surface of the digits (Rehak et al. 1981).
        3. Hyperkeratosis of the elbows, knees, and ankles has been reported in older individuals.
    3. Developmental delay: common
    4. No liver involvement
3. Tyrosinemia, Type III
    1. The rarest of the disorders of tyrosine metabolism
    2. Ambiguous clinical phenotype (Mitchell et al. 2001)
        1. Intellectual disability
        2. Ataxia
        3. Detected on routine screening (Mitchell et al. 2001)
        4. No liver involvement but has skin and ocular changes similar to tyrosinemia, Type II
    3. Hawkinsinuria (a variant of 4-HPPD deficiency)
        1. Affected children may demonstrate chronic acidosis and failure to thrive if fed standard infant formulas or if fed cow's milk as primary nutritional source (Danks et al. 1975).

2. Infants nourished with breast milk: escape symptoms during infancy.

Diagnostic Investigations

1. Clinical laboratory tests (Scott 2006; King et al. 2014)
    1. Tyrosinemia, Type I
        1. Acute early phase: may progress to acute liver necrosis, ascites, jaundice, and gastrointestinal bleeding
            1. Prothrombin and partial thromboplastin times: markedly prolonged.
            2. Other clotting factors: preservation of Factor V and Factor VIII, but decrease in Factors II, VII, XI, XI, and XII.
            3. Liver function tests: modestly elevated transaminase and normal or only slightly elevated serum bilirubin (Mitchell et al. 2001).
            4. Striking biochemical feature: a markedly elevated α-fetoprotein averaging approximately 160,000 ng/ml at the time of diagnosis.
            5. Presence of a characteristic odor of "boiled cabbage" or "rotten mushrooms" and elevation of α-fetoprotein often lead to the clinical recognition of tyrosinemia, Type I, from other causes of acute liver failure; documentation of elevations of plasma tyrosine, methionine, and phenylalanine and succinylacetone in the urine or plasma confirms the diagnosis.
            6. Marked elevation of succinylacetone in the urine or plasma can be considered pathognomonic for tyrosinemia, Type I.
        2. More chronic form of the disorder: renal involvement (major manifestations)
            1. Renal tubular dysfunction involves a generalized aminoaciduria, phosphate loss, and, for many, renal tubular acidosis (Roth et al. 1991).
            2. Renal loss of phosphate is believed to be the mechanism for the development of rickets.
            3. Growth failure is ascribed to the chronic illness from poor nutrition, liver involvement, and/or chronic renal disease.
    2. Tyrosinemia, Type II
        1. Plasma tyrosine levels: typically >500 μM/L, may exceed 1,000 μM/L
        2. Other amino acids: normal including methionine and phenylalanine
        3. Urine organic acids: an increased excretion of *p*-hydroxyphenylpyruvate, *p*-hydroxyphenyllactate, *p*-hydroxyphenylacetate, and small quantities of *N*-acetyltyrosine and 4-tyramine.
    3. Tyrosinemia, Type III
        1. Plasma concentration of tyrosine: from 350 to 650 μM/L.
        2. Increased excretion of 4-hydroxyphenylpyruvic acid, 4-hydroxyphenyllactate, and 4-hydroxyphenylacetate.
        3. The precise quantities vary with protein intake.
2. Imaging (de Laet et al. 2013)
    1. Bone X-ray of the wrist and chest: to define tubulopathy
    2. Ultrasound: to identify echogenicity of the parenchyma and nodular lesions of the liver and monitor kidney growth and changes in renal parenchyma
    3. CT scan with contrast: to identify malignant change of the liver (need a risk-benefit analysis to avoid extra radiation in children)
    4. MRI: best technique to differentiate nodules and carcinomas
3. Molecular genetic analysis for tyrosinemia, Type I
    a. Targeted mutation analysis for the four common FAH pathogenic variants.
    b. Sequence analysis of the entire coding region can detect pathogenic variants in >95% of affected individuals.

Genetic Counseling

1. Recurrence risk
   1. Autosomal recessive inheritance
      1. Patient's sib: each sibling of an affected patient has a 25% chance of being affected, a 50% risk of being an asymptomatic carrier, and a 25% chance of being unaffected and not carrier.
      2. Patient's offspring: not increased unless the spouse is a carrier.
   2. Autosomal dominant inheritance
      1. Patient's sib: each child of an affected individual has a 50% chance of inheriting the mutation.
      2. Patient's offspring: 50%.
2. Prenatal diagnosis (King et al. 2014)
   1. Molecular genetic analysis for tyrosinemia, Type I: If the *FAH* pathogenic variants have been identified in an affected family member, prenatal testing for pregnancies at increased risk may be available from a clinical laboratory that offers either testing of this gene or custom prenatal testing. Prenatal diagnosis of tyrosinemia type 1 using next generation sequencing (Rafati et al. 2016)
   2. Preimplantation genetic diagnosis: an option for some families in which the FAH pathogenic variants have been identified.
3. Management (Scott 2006)
   1. Tyrosinemia, Type I
      1. Artificial formula low in phenylalanine and tyrosine (utilization of a nutritionist skilled in metabolic disorders)
         1. Moderately useful in reducing succinylacetone
         2. Some benefit in the more chronic forms of the disease
         3. Not very effective in acute stage of the disorder in young children
      2. Nitisinone, [2-(2-nitro-4-trifluoromethylbenzoyl)-1,3 cyclohexanedione (NTBC)], which blocks p-hydroxyphenylpyruvic acid dioxygenase (*p*-HPPD) and prevents the accumulation of fumarylacetoacetate and its conversion to succinylacetone
         1. Should begin as soon as the diagnosis is confirmed.
         2. At least 90% of patients with acute form will respond to nitisinone therapy.
         3. Major complications: tyrosine crystal deposition in the cornea, causing photophobia and an ocular inflammatory response. To prevent this, tyrosine concentrations should be monitored and the children utilize a phenylalanine- and tyrosine-restricted diet.
         4. Require long-term monitoring for possible development of hepatocarcinoma (MRI or CT scans of the liver annually).
      3. Prevention/treatment of secondary complications: carnitine deficiency, osteoporosis, and rickets that are secondary to renal tubular Fanconi syndrome
      4. Liver transplantation
         1. Reserved for children who have severe liver failure at presentation and fail to respond to nitisinone therapy
         2. For children who have documented evidence of malignant changes in hepatic tissue
   2. Tyrosinemia, Type II
      1. A low-protein diet and use of a special formula free of phenylalanine and tyrosine: effective in lowering the plasma level of tyrosine to <600 μM
      2. Resolution of both eye and skin symptoms within days to several weeks after institution of the diet and special formula
   3. Tyrosinemia, Type III: a diet low in phenylalanine and tyrosine can lower plasma tyrosine.

References

Danks, D. M., Tippett, P., & Rogers, J. (1975). A new form of prolonged transient tyrosinemia presenting with severe metabolic acidosis. *Acta Paediatrica Scandinavica, 64*, 209–221.

De Laet, C., Dionisi-Vici, C., Leonard, J. V., et al. (2013). Recommendations for the management of tyrosinemia type 1. *Orphanet Journal of Rare Diseases, 8*, 8–16.

Goldsmith, L. A., Kang, E., Bienfang, D. C., et al. (1973). Tyrosinemia with plantar and palmar keratosis and keratitis. *Journal of Pediatrics, 83*, 798–805.

Huhn, R., Stoermer, H., Klingele, B., et al. (1998). Novel and recurrent tyrosine aminotransferase gene mutations in tyrosinemia Type II. *Human Genetics, 102*, 305–313.

King, L. S., Trahms, C., & Scott, C. R. (2014). Tyrosinemia type I. *GeneReviews, 17*, 2014.

Lindblad, B., Lindstedt, S., & Steen, G. (1977). On the enzymic defects in hereditary tyrosinemia. *Proceedings of the National Academy of Sciences of the United States of America, 74*, 4641–4645.

Macsai, M. S., Schwartz, T. L., Hinkle, D., et al. (2001). Tyrosinemia type II: Nine cases of ocular signs and symptoms. *American Journal of Ophthalmology, 132*, 522–527.

Mitchell, G. A., Grompe, M., Lambert, M., & Tanguay, R. M. (2001). Hypertyrosinemia. In C. R. Scriver, A. Beaudet, W. Sly, & D. Valle (Eds.), *The metabolic and molecular bases of inherited disease* (pp. 1777–1805). New York: McGraw-Hill.

Rafati, M., Mohamadhashem, F., Hoseini, A., et al. (2016). Prenatal diagnosis of tyrosinemia type 1 using next generation sequencing. *Fetal and Pediatric Pathology, 35*, 282–285.

Rehak, A., Selim, M. M., & Yadav, G. (1981). Richner–Hanhart syndrome (tyrosinaemia-II) (report of four cases without ocular involvement). *British Journal of Dermatology, 104*, 469–475.

Roth, K. S., Carter, B. E., & Higgins, E. S. (1991). Succinylacetone effects on renal tubular phosphate metabolism: A model for experimental renal Fanconi syndrome. *Proceedings of the Society for Experimental Biology and Medicine, 196*, 428–431.

Scott, C. R. (2006). The genetic tyrosinemias. *American Journal of Medical Genetics Part C (Seminars in Medical Genetics), 142C*, 121–126.

Tomoeda, K., Awata, H., Matsuura, T., et al. (2000). Mutations in the 4-hydroxyphenylpyruvic acid dioxygenase gene are responsible for tyrosinemia type III and hawkinsinuria. *Molecular Genetics and Metabolism, 71*, 506–510.

van Spronsen, F. J., Thomasse, Y., Smit, G. P., et al. (1994). Hereditary tyrosinemia type I: A new clinical classification with difference in prognosis on dietary treatment. *Hepatology, 20*, 1187–1191.

Fig. 1 This 2.5-year-old Palestine girl was seen because of an abnormal newborn screen which showed an abnormal amino acid profile with a succinylacetone level of 3.6 umol/L with a normal being less than 0.40 umol/L. Her alpha-fetoprotein level was greater than 20,000. Her plasma tyrosine was 524 uM with a normal of 28–134. Her urinary organic acid, succinylacetone, was 15 millimoles per mole creatinine which is significantly elevated as normal is zero (0). These results confirmed the diagnosis of tyrosinemia, Type I. Family history showed that the mother's sister has a son and a daughter with tyrosinemia, Type I

Fig. 2 Previous patient at 5 years of age. She had a G-tube placement and gallbladder removed when she was 4. Her Gallbladder was only working 27%, the G-tube was placed to help give her the nutrition she was missing from her diet restriction when her body started to become very weak and ill all the time due to her not drinking her formula. At the age of 3, she was diagnosed with kidney stones and had a stent placed to help remove the stones.