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Tyrosinemia type 1

Prof. Clemens Kamrath, M.D., Ph.D.

Director, Outpatient Clinic for Congenital Metabolic Disorders
Center for Pediatric and Adolescent Medicine
Gießen and Marburg University Medical Center
Gießen Campus
Feulgenstr. 12
35385 Gießen
www.ukgm.de

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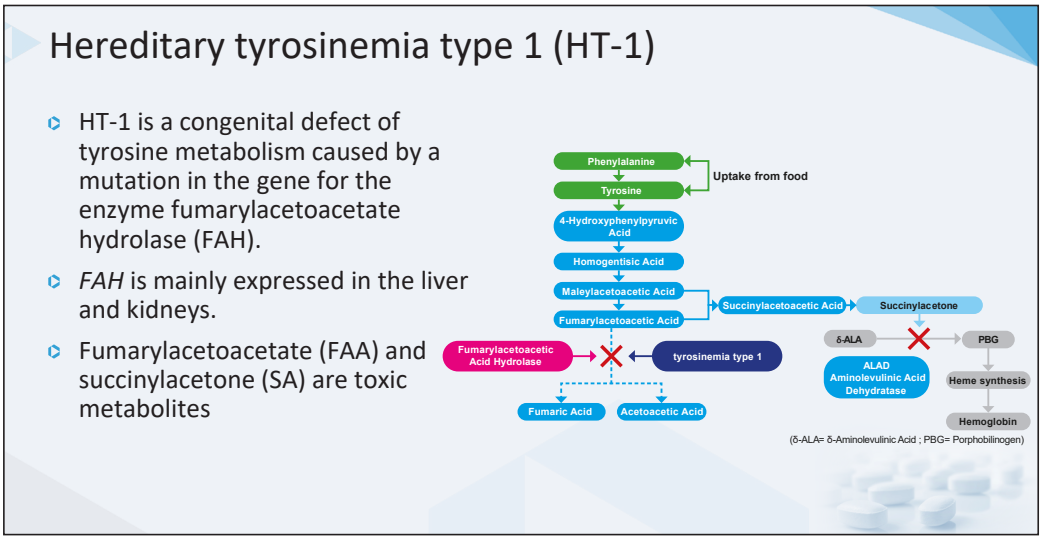

Figure 1

Introduction

Hereditary tyrosinemia type 1 (HT-1) - also known as hepatorenal tyrosinemia (OMIM 276700) - is a rare autosomal recessive metabolic disorder, affecting about one in 100,000 newborns. The disorder is caused by a defect in the last enzyme involved in tyrosine breakdown, fumarylacetoacetate hydrolase (FAH). The FAH deficiency causes the accumulation of the toxic metabolite succinylacetone. The disorder mainly affects the liver, kidneys and peripheral nerves. There are two clinical phenotypes of HT-1: the "acute" type, which becomes symptomatic within the first weeks or months of life and results in liver failure, and the "chronic" type, which is associated with progressive liver disease and an increased risk of hepatocellular carcinoma. If left untreated, HT-1 may be fatal (often before the age of 10 years) due to liver failure.

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Pathophysiology (Figure 1)

The amino acid tyrosine is provided both directly from food and by conversion of phenylalanine through the activity of phenylalanine hydroxylase. Accumulation of metabolites upstream of FAH deficiency is responsible for the clinical effects of the disorder. Succinylacetone is hepatotoxic, tubulotoxic, and neurotoxic, leading to liver injury, renal Fanconi syndrome, and porphyric seizures. The neurologic (porphyric) crises result from direct inhibition of porphobilinogen synthase in heme synthesis with accumulation of δ-aminolevulinic acid.

Symptoms (Figure 2)

Early signs and symptoms of tyrosinemia are usually the result of acute liver injury and may manifest as early as infancy. These include vomiting, diarrhea, abdominal pain, jaundice, bleeding, enlarged liver, and failure to thrive. However, since these symptoms are non-specific and the condition is quite rare, the actual diagnosis is often delayed. Coagulopathy is also a common early sign, which may manifest without other clinical signs of liver dysfunction. However, a continuum of disease severity is possible at presentation, ranging from liver dysfunction and failure within the first few months of life to chronic illness with cirrhosis. Older children and adults may experience symptoms such as fatigue, abdominal pain, weight loss, muscle weakness, and bone problems.

Clinical symptoms usually appear before two years of age, with the majority of children presenting before six months of age with signs of acute liver failure and renal dysfunction with renal tubular dysfunction accompanied by hypophosphatemic rickets and failure to thrive. Neurologic crises may arise at any time and lead to respiratory failure and death. Children with HT-1 are at high risk for hepatocellular carcinoma and this may also be the first clinical event.

Acute peripheral neuropathy associated with episodes of painful dysesthesia or paralysis is a known complication in untreated patients with HT-1 and is caused by axonal degeneration, secondary demyelination, and possibly direct neuronal/synaptic dysfunction of the central nervous system. A mild illness such as a febrile infection may trigger neurologic crises, and these are often accompanied by vomiting or ileus-like symptoms. Typical findings

in neurologic crisis include pain localized to the legs, and occasionally the abdomen, axial and extensor hypertonia, marked weakness (which may require mechanical ventilation), hyponatremia (sometimes associated with seizures), and hypertension.

Natural course of the disorder

Without early diagnosis and specific treatment, tyrosinemia type 1 will result in severe complications and death. Before the approval of nitisinone (nitisinone was approved as an orphan drug in the EU in 2005 for the treatment of tyrosinemia type 1), 90% of HT-1 patients died within the first two years of life. Advanced symptoms included liver failure, kidney damage with the development of tubulopathy culminating in Fanconi syndrome, neurologic problems such as delayed development, muscle spasms, and mental retardation. Consequences of renal tubule dysfunction include hypophosphatemic vitamin D-resistant rickets, hyperaminoaciduria, renal tubular acidosis due to loss of bicarbonate, proteinuria, and short stature. In the long term, about 25-30% of affected children developed hepatocellular carcinoma.

Until the early nineties, the only available strategies for treating patients with HT-1 were a low-protein diet with reduction in phenylalanine and tyrosine and liver transplantation for liver failure or hepatocellular carcinoma. However, the efficacy of these strategies has been disappointing in some cases. For example, the one-year survival rate for infants placed on a low-protein diet before six months of age was only about 50%.

Treatment

The introduction of nitisinone (2-[2-nitro-4-trifluoromethylbenzoyl]-1,3-cyclohexanedione; NTBC) as a specific treatment for HT-1 has fundamentally altered the clinical course and prognosis of individuals affected by HT-1.

Studies have demonstrated that nitisinone is a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, which catalyzes the conversion of 4-hydroxyphenylpyruvate to homogentisic acid in the catabolic breakdown pathway of tyrosine. By blocking the proximal tyrosine breakdown pathway, nitisinone inhibits the formation of the toxic metabolite succinylacetone in patients with tyrosinemia type 1.

However, in order to achieve the best long-term outcomes, effective drug treatment requires early identification of affected children. Timely diagnosis and early initiation of treatment in the neonatal period with nitisinone and nutritional support are critical for prognosis, especially regarding the advent of complications such as hepatocellular carcinoma and neurocognitive impairment.

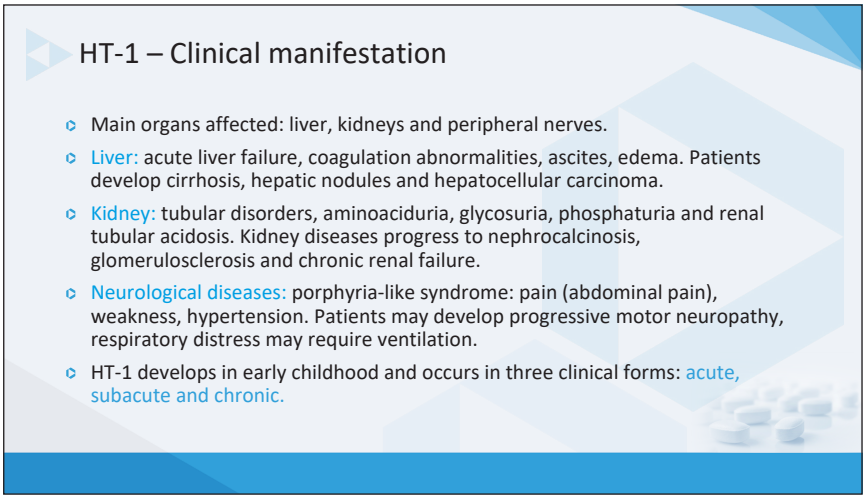


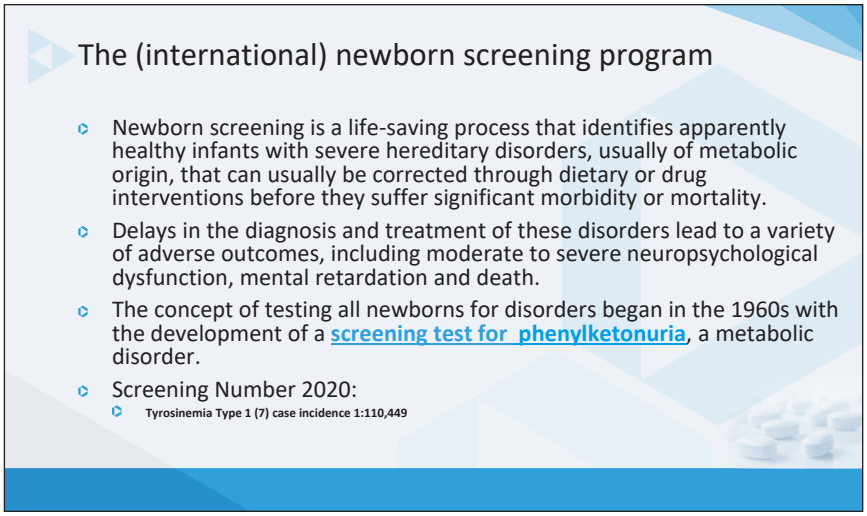
Figure 2

Screening of newborns for tyrosinemia type 1 (Figure 3)

A purely clinical diagnosis in early life is not helpful because of the latency of symptom onset and the sometimes nonspecific nature of the symptoms. Initial attempts at screening newborns to detect presymptomatic infants with HT-1 by measuring tyrosine levels proved diagnostically unreliable. Succinylacetone from dry blood demonstrates extremely high sensitivity and specificity for the disorder and has become a reliable marker for the identification of affected newborns.

The introduction of a newborn blood testing program for HT-1 not only requires a simple, safe, accurate, and validated screening test, but also proof that treatment in the presymptomatic phase results in better outcomes for the tested patients than treatment after symptom onset. A number of cohort studies (including in Quebec and the United Kingdom) have found a clear benefit for earlier versus later treatment. Newborn screening for tyrosinemia type 1 by quantification of succinylacetone employing tandem mass spectrometry has been performed nationwide in Germany since March 16, 2018, and allows early diagnosis of HT-1 at an asymptomatic stage. Identification of biallelic pathogenic variants in the FAH gene confirms the diagnosis of tyrosinemia type 1. With early and

Figure 3



correct identification and appropriate medical treatment, the majority, if not all, affected newborns with HT-1 can be expected to live without liver or kidney disease.

If treatment is started within the first weeks of life, liver and kidney dysfunction will not arise and the development of hepatocellular carcinoma can be prevented in most cases. Treatment comprises drug therapy with nitisinone in combination with a low-protein diet supplemented with an amino acid mixture free of tyrosine and phenylalanine. In cases of strongly suspected tyrosinemia type 1, such as an abnormal finding on neonatal screening with elevated succinylacetone levels, children with tyrosinemia type 1 should be treated immediately with nitisinone, even if the genetic diagnostic work-up is not yet available. The initial dose is 1 (-2) mg/kg body weight daily. Treatment aims to lower succinylacetone to within the normal range or below the limit of detection. Nitisinone plasma levels should be around 30-60 µmol/L. Normalization of liver and kidney function can be expected with nitisinone treatment. Liver function tests including coagulation (PT, aPTT) should be routinely performed as an indication of early HT-1 associated liver disease. In addition, complete blood counts should be obtained on a regular basis, as transient thrombocytopenia and leukopenia may develop during treatment.

Nutritional therapy in tyrosinemia type 1

Nutritional management in patients treated with nitisinone has two goals:

- To restrict the amino acids phenylalanine and tyrosine
- To ensure that essential amino acids and micronutrients are supplied as needed.

Since about 75% of dietary phenylalanine is converted to tyrosine, phenylalanine must be reduced in the diet of affected patients.

In order to achieve dual restriction of phenylalanine and tyrosine, the amount of intact dietary protein prescribed should be reduced from that recommended for age. To meet protein, energy and nutrient needs, it is necessary to consume medical foods that are amino acid blends free of phenylalanine and tyrosine. In addition, modified low-protein foods are another manufactured source of a diet low in phenylalanine and tyrosine.

Hepatocellular carcinoma

The level of alpha-fetoprotein is routinely determined for monitoring the possible development of hepatocellular carcinoma. Alpha-fetoprotein levels often remain elevated for a prolonged period after treatment has begun, and failure to return to normal or a secondary elevation is cause for imaging studies. Primarily, abdominal ultrasonography follow-up should be performed every 6 - 12 months. However, magnetic resonance imaging has a higher sensitivity and specificity. Liver biopsies should be avoided because of the risk of tumor cell dissemination.

Summary

Tyrosinemia is a rare but serious genetic metabolic disorder requiring lifelong treatment. Early diagnosis and adequate treatment are critical to minimize complications and improve the quality of life of those affected. From the literature evolving over the past decade, it appears that early use of nitisinone has significantly improved the prognosis for patients with HT-1. Complications previously associated with HT-1, including early death, liver failure, painful and threatening neurologic crises, progressive renal dysfunction with hypophosphatemic rickets, and early development of hepatocellular carcinoma, can be minimized or even eliminated by identifying affected neonates early and initiating drug treatment and a dietary regimen within the first four weeks of life, and then implementing and continuing them consistently. This can only be accomplished through a neonatal screening program. It remains to be seen whether the prevention of hepatocellular carcinoma will persist into adulthood.

Current research is helping to advance treatment options and provide hope for patients with severe inborn errors of metabolism.

Contact

■ **Prof. Clemens Kamrath, M.D., Ph.D.**
Director, Outpatient Clinic for Congenital Metabolic Disorders
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Feulgenstr. 12
35385 Gießen
www.ukgm.de

Additional information
www.DIPHARMA-Arzneimittel.de