NORD Guides for Physicians #1

The National Organization for Rare Disorders

Physician's Guide to Tyrosinemia Type 1

NORD
National Organization for Rare Disorders

The original version of this booklet was made possible by donations in honor of Danielle Barckett. Now 15, Danielle was one of the first patients to receive an experimental treatment for tyrosinemia that is now considered standard therapy.

This booklet is the first in a series of free publications for physicians and other medical professionals. It is NORD's hope that patients and their families will benefit from this and other efforts to enhance awareness of the almost 7,000 rare diseases affecting an estimated 30 million Americans.

NORD gratefully acknowledges the assistance of the following physician in the preparation of this publication:

ROBERT M. TANGUAY, D.Sc.
Professor and Associate Head, Department of Molecular Biology, Medical Biochemistry and Pathology
Laval University, Quebec

What is tyrosinemia type I?

Tyrosinemia type 1 is a rare genetic metabolic disorder characterized by lack of the enzyme fumarylacetoacetate hydrolase (FAH), which is needed to break down the amino acid tyrosine. Failure to properly break down tyrosine leads to abnormal accumulation of tyrosine and its metabolites in the liver, resulting in severe liver disease. Tyrosine may also accumulate in the kidneys and central nervous system.

Metabolic disorders are disorders that affect the body's ability to perform certain chemical processes such as turning food into energy or recycling waste from dead cells. Many metabolic disorders do not have noticeable signs or symptoms at birth, but can eventually cause serious physical problems if not detected and treated early. There are three types of tyrosinemia. This booklet describes type 1.

Recent advances regarding tyrosinemia type 1 have dramatically improved the overall prognosis of this disorder in infants and children who receive a prompt diagnosis and early treatment. Combined therapy with the drug nitisinone and a low-protein diet has increased the survival rate of affected children to greater than 90 percent.

What symptoms are associated with untreated tyrosinemia type 1?

If untreated, this disorder can potentially result in a wide variety of symptoms. Specific symptoms associated with tyrosinemia type 1 often vary greatly from one person to another. Individuals with tyrosinemia type 1 typically present with either an acute or chronic form of the disorder.

The so-called acute form is present at birth or during the few first months of life. Infants with the acute form of tyrosinemia type 1 exhibit rapid onset of symptoms, usually beginning with failure to thrive. Additional early symptoms include:

- Fever
- Diarrhea/bloody stools
- Vomiting
- Enlarged liver
- Tendency to bruise easily
- Jaundice
- Lethargy
- Irritability
- Some infants may have a distinctive cabbage-like odor to the skin and urine

Eventually, infants with the acute form of tyrosinemia type I may experience:

- Developmental delays
- Enlarged spleen
- Accumulation of fluid (edema) in the abdomen (ascites)
- Kidney disease
- Blood clotting abnormalities causing frequent nosebleeds and gastrointestinal bleeding

When untreated, tyrosinemia type 1 often rapidly progresses to acute life-threatening liver failure.

The chronic form of tyrosinemia type 1 occurs less frequently than the acute form and is generally characterized by a more gradual onset and less severe expression of the symptoms. Initial signs may include vomiting, diarrhea, and enlarged liver and spleen, and failure to thrive. Infants with the chronic form may eventually develop:

- Progressive cirrhosis of the liver resulting in chronic liver failure
- Developmental delays
- Renal Fanconi syndrome, a rare disorder characterized by kidney dysfunction, weakness and softening of the bones (rickets) and episodes of vomiting, dehydration, weakness and fever

Additional symptoms occur in infants with tyrosinemia type 1. Affected infants may have repeated, neurologic episodes (neurologic crises) lasting one to seven days. These episodes may go unrecognized, but are characterized by:

- Acute polyneuropathy – characterized by severe pains in the legs
- Altered mental status
- Abdominal pain
- Respiratory failure

Infants and children with tyrosinemia type I are also at a greater risk than the general population of developing a form of liver cancer known as hepatocellular carcinoma.

In rare cases, hypertension and hypertrophic cardiomyopathy (heart muscle weakness) have been reported.

How is tyrosinemia type 1 diagnosed?

Today, tyrosinemia type 1 is often diagnosed as a result of newborn screening. Most states now screen all newborns for tyrosinemia.

A diagnosis of tyrosinemia type 1 is confirmed based upon a thorough clinical evaluation and specialized tests. If not detected by newborn screening, tyrosinemia type 1 may be suspected in infants who display failure to thrive and an enlarged liver during the first three months of life. Diagnosis may be confirmed through the detection of succinylacetone in the urine or decreased activity of the FAH enzyme in liver tissue or cultured fibroblasts.

Prenatal diagnosis of tyrosinemia type 1 is possible through detection of succinylacetone in the amniotic fluid or measurement of fumarylacetoacetase in amniotic fluid cells.

Why is early detection of tyrosinemia type 1 important?

Prompt identification and treatment (e.g., medication and dietary restrictions) may prevent serious liver, kidney and neurological complications. Children will also usually experience normal growth.

What causes tyrosinemia type 1?

Tyrosinemia type 1 is caused by mutations of the *FAH* gene. This gene is responsible for the production of the enzyme fumarylacetoacetate hydrolase. This gene mutation is inherited as an autosomal recessive trait.

In recessive disorders, the condition does not occur unless an individual inherits the same defective gene for the same trait from each parent. A child who receives one normal gene and one gene for the disease will be a carrier but usually will not show symptoms. The risk of transmitting the disease to the children of a couple, both of whom are carriers for a recessive disorder, is 25 percent. Fifty percent of their children risk being carriers of the disease but generally will not show symptoms of the disorder. Twenty-five percent of their children may receive both normal genes, one from each parent, and will be genetically normal for that trait. The risk is the same for each pregnancy.

The symptoms of tyrosinemia type 1 are caused by the accumulation of tyrosine and its metabolites (i.e., succinylacetoacetate, succinylacetone and fumarylacetone) in the liver, kidneys and central nervous system.

Who gets tyrosinemia type 1?

Tyrosinemia type 1 affects males and females in equal numbers. It is estimated to occur in one of every 100,000-120,000 births in the United States. In one region of the Quebec province of Canada, the disorder is estimated to occur in approximately one in 1,850 births. The birth prevalence is also higher in Norway where it is estimated to be one in 60,000.

How is it treated?

Individuals with tyrosinemia type 1 are treated with a combination of medication and diet. Three main options exist for the treatment of tyrosinemia type 1:

Medication: The U.S. Food and Drug Administration (FDA) has approved the orphan drug nitisinone (Orfadin®) to treat tyrosinemia type 1. This drug is a protein inhibitor of 4-hydroxyphenylpyruvate dioxygenase that reduces the formation of toxic metabolites associated with tyrosinemia type 1. It should be administered by a physician with experience treating tyrosinemia type 1 as the dosage must be tailored to each individual. Nitisinone increases the blood concentration of tyrosine and, consequently, must be used in conjunction with a diet restricted in the amino acids tyrosine and phenylalanine.

Treatment with nitisinone and proper dietary management should start immediately after a diagnosis of tyrosinemia type 1 is confirmed. Nitisinone is marketed by Rare Disease Therapeutics, Inc. For information about the drug, contact:

Rare Disease Therapeutics, Inc.
2550 Meridian Blvd.
Suite 150
Franklin, TN 37067
Tel: (615) 399-0700 Fax: (615) 399-1217
www.raretx.com

Diet: Infants with tyrosinemia type 1 should be placed on a low protein diet that contains limited amounts of phenylalanine and tyrosine. In some cases, affected infants have exhibited improvement of liver and kidney abnormalities with dietary management alone. However, progression to cirrhosis, liver failure and potential liver cancer is still possible. Therefore, affected individuals must observe a very strict diet using special medical foods throughout their lifetime.

Liver transplant: Liver transplantation may be required in cases where affected infants or children develop end stage liver failure, fail to respond to therapy with nitisinone, or have evidence of liver cancer.

Genetic counseling will be of benefit for families of children with tyrosinemia.

Does tyrosinemia type 1 go by other names?

In the past, tyrosinemia type 1 was also known as "hereditary infantile tyrosinemia" and "hepatorenal tyrosinemia."

NORD Guides for Physicians #1

#1 The Physician's Guide to Tyrosinemia Type 1

#2 The Pediatrician's Guide to Ornithine Transcarbamylase Deficiency…and other Urea Cycle Disorders

#3 The Physician's Guide to Primary Lateral Sclerosis

#4 The Physician's Guide to Pompe Disease

#5 The Physician's Guide to Multiple System Atrophy

#6 The Physician's Guide to Hereditary Ataxia

#7 The Physician's Guide to Giant Hypertrophic Gastritis and Menetrier's Disease

#8 The Physician's Guide to Amyloidosis

#9 The Physician's Guide to Medullary Thyroid Cancer

#10 The Physician's Guide to Hereditary Angioedema (HAE)

#11 The Physician's Guide to The Homocystinurias

These booklets are available free of charge. To obtain copies, call or write to NORD or download the text from www.rarediseases.org

This booklet was made possible by a charitable contribution from Rare Disease Therapeutics. The series is intended to increase awareness of rare diseases and available resources. For additional copies, contact NORD.

For information on rare disorders and the voluntary health organizations that help people affected by them, visit NORD's Web site at www.rarediseases.org or call (800) 999-NORD or (203) 744-0100.

NORD helps patients and families affected by rare disorders by providing:

- Physician-reviewed information in understandable language
- Referrals to support groups and other sources of help
- Networking with other patients and families
- Patient assistance programs
- Grants and fellowships to encourage research on rare diseases
- Advocacy for health-related causes that affect the rare-disease community
- Publications for physicians and other medical professionals

Contact NORD at:
orphan@rarediseases.org.

National Organization for Rare Disorders (NORD)
PO Box 1968
Danbury, CT 06813-1968
Phone: (203) 744-0100
Tollfree: (800) 999-NORD
Fax: (203) 798-2291