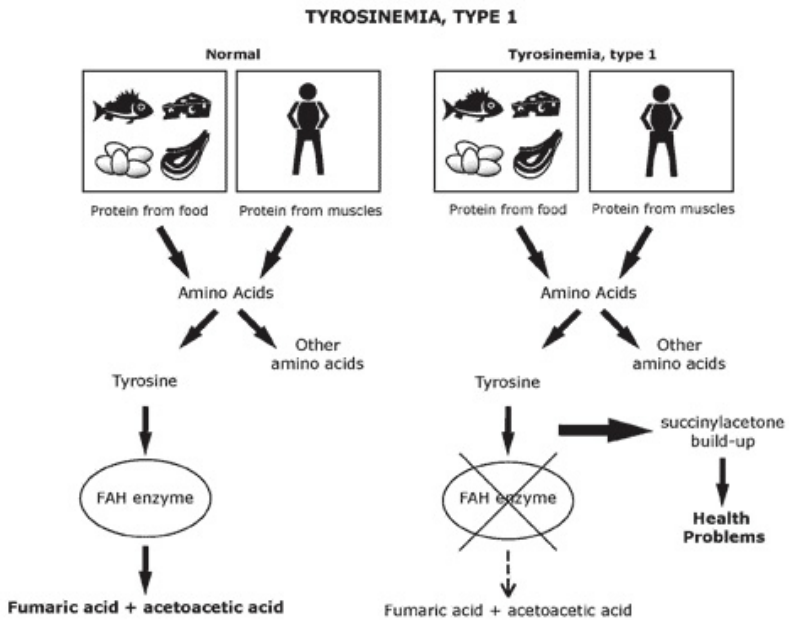
TYROSINEMIA
INFORMATION FOR PARENTS/CARERS

What is Tyrosinemia?

This condition is one type of amino acid disorder. People with tyrosinemia have problems breaking down an amino acid called tyrosine from the food they eat. If not treated, the condition causes severe liver disease and other serious health problems.



Elevated blood tyrosine levels are associated with several clinical entities. The term tyrosinemia was first given to a clinical entity based on observations (eg, elevated blood tyrosine levels) that have proven to be common to various disorders, including transient tyrosinemia of the newborn (TTN), hereditary infantile tyrosinemia (tyrosinemia I), Richner-Hanhart syndrome (tyrosinemia II), and tyrosinemia III.

What causes tyrosinemia?

In order for the body to use protein from the food we eat, it is broken down into smaller parts called amino acids. Special enzymes then make changes to the amino acids so the body can use them.

Tyrosinemia type I occurs when an enzyme, called fumarylacetoacetase (FAH), is either missing or not working properly. When FAH is not working, it cannot break down tyrosine. Tyrosine and other harmful substances then build up in the blood. One of these substances is called succinylacetone. When it builds up in the blood, it causes serious liver and kidney damage. It may also cause episodes of weakness or pain.

Type II tyrosinemia is caused by a deficiency of the enzyme tyrosine amino-transferase. Tyrosine aminotransferase is the first in a series of five enzymes that converts tyrosine to smaller molecules, which are excreted by the kidneys or used in reactions that produce energy. This form of the disorder can affect the eyes, skin, and mental development.

Type III tyrosinemia is a rare disorder caused by a deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase. This enzyme is abundant in the liver, and smaller amounts are found in the kidneys. It is one of a series of enzymes needed to break down

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tyrosine. Specifically, 4-hydroxyphenylpyruvate dioxygenase converts a tyrosine byproduct called 4-hydroxyphenylpyruvate to homogentisic acid.

What are the symptoms of Tyrosinemia?

Symptoms of type I tyrosinemia usually appear in the first few months of life and include failure to gain weight and grow at the expected rate (failure to thrive), diarrhea, vomiting, yellowing of the skin and whites of the eyes (jaundice), cabbagelike odor, and increased tendency to bleed (particularly nosebleeds). Type I tyrosinemia can lead to liver and kidney failure, problems affecting the nervous system, and an increased risk of liver cancer.

Symptoms of type II tyrosinemia often begin in early childhood and include excessive tearing, abnormal sensitivity to light (photophobia), eye pain and redness, and painful skin lesions on the palms and soles. About half of individuals with type II tyrosinemia are also mentally retarded. Type II tyrosinemia occurs in fewer than 1 in 250,000 individuals.

Symptoms of type III Tyrosinemia includes mild mental retardation, seizures, and periodic loss of balance and coordination (intermittent ataxia). Type III tyrosinemia is very rare; only a few cases have been reported.

How do doctors diagnose tyrosinemia?

Because Tyrosinemia must be treated early, babies must be routinely tested for the disease. A small blood sample is taken from the baby's heel or arm and checked in a laboratory for high levels of tyrosine.

What is the treatment for tyrosinemia?

Your baby's doctor will work with a metabolic doctor and dietician to care for your child. Lifelong treatment is usually needed to prevent liver and kidney problems. Treatment consists of medication and a diet low in tyrosine and another amino acid called phenylalanine (phe). The low-tyrosine/phenylalanine diet is made up of a special medical formula and carefully chosen foods. You must start the treatment as soon as you know your child has the condition.

The following treatments are often recommended for children with tyrosinemia 1:

1. Medication

A medication called Nitisinone (Orfadin®), also known as NTBC, is used to prevent liver and kidney damage. It also stops the neurologic crises. The medication may also lessen the risk for liver cancer. Your child should start taking Nitisinone as soon as possible. Your doctor will need to write a prescription for this medication. Vitamin D is sometimes used to treat children who have rickets. Do not take any medication without talking with your doctor.

2. Medical Formula

The special medical formula gives babies and children the nutrients and protein they need

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while helping keep their tyrosine levels within a safe range. Your metabolic doctor and dietician will tell you what type of formula is best and how much to use.

3. Low-tyrosine / phenylalanine diet:

The diet is made up of foods that are very low in tyrosine and phenylalanine. This means your child will need to limit foods such as cow's milk and regular formula. He or she will need to avoid meat, eggs and cheese. Regular flour, dried beans, nuts and peanut butter contain these amino acids and must also be limited.

Many vegetables and fruits have only small amounts of phenylalanine and tyrosine and can be eaten regularly in carefully measured amounts. There are other medical foods such as special flours, pastas, and rice that are made especially for people with tyrosinemia 1. Some states offer help with payment, or require private insurance coverage for formula and other special medical foods. Your metabolic doctor and dietician will decide on the best food plan for your child. The exact plan will depend on many things such as your child's age, weight, general health, and how well the medication is working. Your dietician will fine-tune your child's diet over time.

4. Blood, urine and other tests

Your child will have regular blood and urine tests to check:

- amino acid levels
- the amount of succinylacetone

These tests help your doctor and dietician figure out whether any changes to the medication or diet are needed. Some experts suggest that children with tyrosinemia 1 have a CT or MRI scan of their liver once a year to check for scarring or cancer.

5. Liver transplantation

Before nitisinone was available, liver transplantation was one of the main treatments for tyrosinemia 1. Now, nitisinone can prevent or reverse many of the liver problems. More time is needed to see if this medication can prevent liver cancer. For most children, nitisinone will delay, and hopefully prevent, the need for liver transplant.

Liver transplantation is still an option to prevent liver cancer. It may also be considered for children who show signs of liver cancer or liver failure. If you have questions, talk to your metabolic doctor or doctor about the benefits and risks of transplantation.

If tyrosinemia 1 is not treated, what problems occur?

The symptoms can vary a great deal from person to person. There are two types of tyrosinemia 1. The more common form happens in infants. The less common form is seen in older children and adults.

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Tyrosinemia 1 in infants:

Babies usually show effects of the condition within the first few months of life. Some of the first symptoms may be:

- diarrhea and bloody stools
- vomiting
- poor weight gain
- extreme sleepiness
- irritability
- "cabbage-like" odor to the skin or urine

Liver problems are common. They can lead to:

- enlarged liver
- yellowing of the skin
- tendency to bleed and bruise easily
- swelling of the legs and abdomen

Kidney problems also happen and can lead to:

- rickets, a bone thinning condition
- delays in walking

Without prompt and careful treatment, babies with severe liver and kidney problems usually die. Some babies also have episodes that include:

- pain or weakness, especially in the legs
- breathing problems
- rapid heartbeat
- seizures
- coma, sometimes leading to death

Tyrosinemia 1 in children ("chronic" form):

Children with the chronic form usually start having symptoms after two months of age. Some of the first signs may be trouble gaining weight and episodes of vomiting and diarrhea. Over time, the condition can cause liver, kidney and nerve problems.

- Liver: If the condition is not treated, a rare type of liver scarring called nodular cirrhosis can happen. This gets worse over time and can lead to liver failure. If not treated, many children develop liver failure or liver cancer before the age of 10. Medication, when started early, can prevent liver failure in most children.

- Kidneys: Serious kidney problems can occur in untreated children. When the kidneys are not working properly, episodes of vomiting, weakness and fever can happen. Rickets, a bone thinning condition, may happen in children with kidney damage. Medication can prevent kidney problems in most children.

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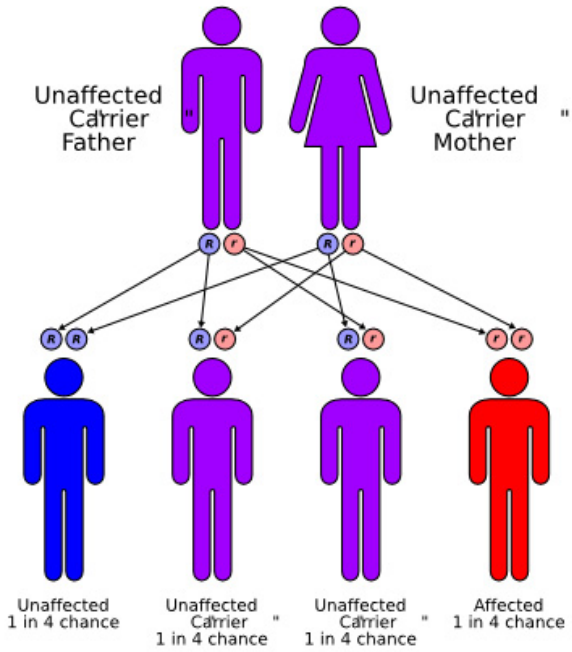
- Neurologic crises: Some children have episodes of weakness, pain or numbness in their arms, legs or other parts of the body. Breathing problems and rapid heartbeat may also happen. Some children have seizures that can lead to coma. Medication can stop episodes of neurologic crisis in most children.
- Other: A small number of children have had heart problems. Some have had high blood pressure.

What happens when tyrosinemia is treated?

When treatment is started early, severe liver, kidney, and neurologic symptoms can be prevented. Children who are treated usually have normal growth and intelligence.

If treatment is not started right away, children may have some liver or kidney damage. Rickets may already be present and need to be treated. Delays in growth and development may also be present. The effects of delayed treatment vary from child to child.

How is tyrosinemia inherited?



This condition is inherited in an autosomal recessive manner. It affects both boys and girls equally.

Everyone has a pair of genes that make the enzyme. In children with tyrosinemia, neither of these genes works correctly. These children inherit one non-working gene for the condition from each parent.

Parents of children with tyrosinemia rarely have the condition themselves. Instead, each parent has a single non-working gene for the condition. They are called carriers. Carriers do not have the condition because the other gene of this pair is working correctly.

When both parents are carriers, there is a 25% chance in each pregnancy for the child to have tyrosinemia. There is a 50% chance for the child to be a carrier, just like the parents. And, there is a 25% chance for the child to have two working genes

Genetic Counseling is available to families who have children with tyrosinemia. Genetic counselors can answer your questions about how the condition is inherited, choices during future pregnancies, and how to test other family members. Ask your doctor about a referral to a genetic counselor.

Can other members of the family have tyrosinemia or be carriers?

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Having tyrosinemia

If they are healthy and developing normally, older brothers and sisters of a baby with tyrosinemia are unlikely to be affected. However, finding out whether other children in the family have this condition may be important. Early treatment can prevent serious health problems. Ask your metabolic doctor whether your other children should be tested.

Where can I find more information?

About Tyrosinemia: New Parents' Guide

http://depts.washington.edu/tyros/abouttyr.htm

Tyrosinemia Parent Support Group

http://groups.msn.com/tyrosinemia

National Urea Cycle Disorders Foundation

http://www.nucdf.org/

Children Living with Inherited Metabolic Diseases (CLIMB)

http://www.climb.org.uk

National Coalition for PKU and Allied Disorders

http://www.pku-allieddisorders.org/

Genetic Alliance

http://www.geneticalliance.org

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