WHAT IS TYPE II TYROSINEMIA?

Type II tyrosinemia is an inborn error of tyrosine metabolism caused by a deficient activity of the enzyme tyrosine aminotransferase (TAT). As a result of this defect tyrosine accumulates in plasma, urine and tissues, causing corneal ulcers and palmoplantar hyperkeratosis. This disease is also known as oculocutaneous tyrosinemia or Richner-Hanhart syndrome, because the symptoms were first described by these two doctors in 1938 and 1947, respectively.

WHAT IS TYROSINE?

Tyrosine is an amino acid found in proteins (long chains of amino acids). It can be either synthesized from phenylalanine or formed directly by the degradation of dietary proteins. Tyrosine is normally metabolized through a series of enzymatic reactions and is converted into energy in the Krebs cycle.

WHAT HAPPENS IN TYROSINEMIA II?

Type II tyrosinemia is caused by the deficiency of the hepatic pyridoxine-dependent enzyme tyrosine aminotransferase (TAT). Due to this deficiency, tyrosine accumulates in plasma, urine and tissues.

Moreover and due to high tyrosine concentrations, other compounds such as tyrosine derivatives (tyramine) and p-OH-phenylpyruvate derivatives, which are synthesized...

WHAT CAUSES TAT DEFICIENCY?

TAT deficiency is caused by mutations (stable and hereditary changes) in the TAT gene, which encodes this enzymatic protein.

Tyrosinemia II is an autosomal recessive disorder, i.e. both parents are carriers of a mutation in the TAT gene, although they do not suffer any clinical symptoms. If both parents transmit the mutated gene to the baby, he/she will suffer a tyrosinemia type II.
WHAT HAPPENS WHEN AN INFANT IS BORN WITH TYROSINEMIA II?

Even though the mother is a carrier of this wrong genetic information, the baby is born without problems since she metabolizes the proteins correctly until birth. When the child starts to be fed, milk proteins break and release all the amino acids.

Tyrosine is not properly degraded due to the enzymatic TAT defect and it starts to accumulate in biological fluids and tissues.

The child may develop ocular symptoms such as redness, tearing, photophobia and pain after two weeks of life or later on. Long-term consequences include corneal opacities, decreased visual acuity, astigmatism, strabismus, and glaucoma, as well as dendritic ulcers due to deposition of tyrosine (highly insoluble) crystals in the cornea. Corneal cells become disrupted and initiate an inflammatory response. These alterations do not respond to conventional treatment.

The cutaneous symptoms consist of hyperkeratosis palmoplantaris which usually begins after the first year of life, however in some cases it can occur from the first month. The hyperkeratotic plaques are progressive, painful (may even prevent ambulation) and nonpruritic (not itchy) and are associated with hyperhidrosis.

Occasionally, some degree of intellectual disability has been described in some patients. Clinical symptoms may vary even in individuals of the same family.

HOW IS TYPE II TYROSINEMIA DIAGNOSED?

Diagnosis is based on clinical suspicion, and is confirmed by amino acid determination in plasma and urine, which shows elevated levels of tyrosine. Occasionally a slight increase in phenylalanine can be found. Organic acid analysis shows high excretion of tyrosine and p-OH-phenylpyruvate derivatives in the absence of succinylacetone, which allows differential diagnosis tyrosinemia type I, far more frequent.

Expanded neonatal screening currently performed in many countries, allows the detection of tyrosinemia II in the first days of life before the first clinical signs and symptoms appear.

TAT is only expressed in the liver, a liver biopsy to demonstrate the enzyme deficiency is not warranted. Therefore the diagnosis is confirmed by genetic studies.

WHAT CAN BE DONE TO AVOID THE CONSEQUENCES OF TYROSINEMIA II?

The diagnosis has to be established as soon as possible and the specific treatment started at once. Treatment basically consists in preventing the accumulation of tyrosine.

This will be achieved by restricting the natural proteins of the diet since all of them contain the precursor amino acids (phenylalanine and tyrosine).

However, amino acids are essential for the synthesis of proteins that will make up the body of the baby. Therefore proteins must be provided by means of a special formula, free in tyrosine and phenylalanine.
Type II tyrosinemia is a hereditary disorder, which if left untreated, can lead to serious consequences. However, if the disorder is rapidly diagnosed and adequately treated, the clinical symptoms are prevented and affected children will enjoy a good quality of life.

**Treatment of tyrosinemia II**

- **Ocular signs**
- **Cutaneous signs**

**Reduction of natural protein intake + special formula**

**Translation**
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