Tyrosine Metabolism Disorders

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The most frequent tyrosine metabolism disorders (Rezmani 2007; Dionisi-Vici et al. 2000; Held 2006) are as follows:

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- Hawkinsinuria
- Alkaptonuria

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5.1 Tyrosinaemia Type I (Tyrosinosis)

The defect is caused by absence or considerably decreased activity of fumarylacetoacetate hydrolase resulting in elevated levels of plasma tyrosine and accumulation of tyrosine metabolites, especially succinylacetone. The disease can have an acute or chronic course. In cases of acute tyrosinosis of infants, they die within 6–8 months due to hepatic failure, if they are not treated. In the chronic form, cirrhosis develops as well as renal injury and involvement of peripheral nerves. Hepatomas are frequent. Tyrosinaemia type I is a genetic disease with autosomal recessive inheritance; therefore, hepatic and renal injury cannot be removed completely. However, the signs can be mitigated by food with low content of tyrosine and phenylalanine. Nitisinone (Orfadin) has been recently authorised for the treatment of tyrosinaemia type I. This treatment together with restrictive diet can successfully reduce disease symptoms, and it enables the children to develop and live normally.

5.2 Tyrosinaemia Type II (Richner-Hanhart Syndrome)

The defect is caused by deficiency of cytosolic hepatic tyrosine aminotransferase, whereas the mitochondrial isoenzyme has normal activity. Enzyme defect results in elevated plasma levels of tyrosine and its elevated urine concentration. Tyrosine is the only amino acid that is elevated in urine. Clinical manifestation is characterised with multiple malformations (microcephaly, corneal changes), erythema, palmar and plantar hyperkeratosis and disorder of mental development. In contrast to tyrosinaemia type I, hepatic and renal functions are normal. The therapy consists of lower intake of aromatic amino acids and proteins. This diet results in normalisation of the concentration of tyrosine and tyrosine metabolites in plasma and urine. Early initiation of the treatment prevents the changes on eyes and skin. The disease has autosomal recessive inheritance.

5.3 Tyrosinaemia Type III

Tyrosinaemia type III has autosomal recessive inheritance. Dysfunction of p-hydroxyphenylpyruvate dioxygenase in the liver and kidneys leads to neurologic disorders and mental retardation of affected persons. This disease is very rare, and it requires restriction of tyrosine and phenylalanine in food.

5.4 Transient Hypertyrosinaemia of the Newborn

The biochemical cause of this anomaly is delayed maturation of liver parenchyma which is associated with delayed maturation of 4-hydroxyphenylpyruvate dioxygenase. The enzyme biosynthesis – and thus the enzyme activity – normally

increases at the end of fetal development; however, it can be delayed in some newborns. Other factors that affect prolonged hypertyrosinaemia in newborns are high content of tyrosine in milk food and lack of vitamin C. Excessive amounts of ingested tyrosine as well as lack of vitamin C result in formation of hydroxyphenylpyruvate that inhibits the enzyme in the liver of the newborns. Hypertyrosinaemia of the newborns is considered harmless, and it usually regresses spontaneously during the first weeks of life as soon as the intake of proteins decreases and vitamin C is administered. The disease is found in 30 % of premature babies and in 10 % of mature newborns.

5.5 Hawkinsinuria

This rare metabolic disorder is caused by heterogeneous mutation of the gene for hydroxyphenylpyruvate dioxygenase that results in enzyme deficiency. Various metabolites of phenylalanine appear in urine: p-hydroxyphenylpyruvate, p-hydroxyphenylacetate and a special amino acid called hawkinsin. The disease is manifested in childhood after increased caloric load by acidosis, ketosis, hepatomegaly and transient tyrosinaemia. The condition regresses after restriction of tyrosine and phenylalanine intake. This disease has autosomal dominant inheritance.

5.6 Alkaptonuria

Alkaptonuria is caused by deficiency of homogentisate 1,2-dioxygenase (HGD) – the enzyme that is the part of metabolic pathway of degradation of aromatic amino acids phenylalanine and tyrosine (Fig. 4.3). Homogentisate that is excreted in urine is subsequently oxidised by air oxygen to brown-black pigment called alkapton. Another sign in older age is ochronosis – pigmentation of connective tissues (cartilages). The mechanism of ochronosis development consists in oxidation of homogentisate by polyphenoloxidase with the formation of benzoquinone acetate, which polymerises and binds to macromolecules of connective tissues. Inheritance and clinical manifestations of alkaptonuria are described in the next chapters.

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