SUMMARY

Phenylketonuria (PKU) is a metabolic disorder affecting the metabolism of essential aromatic amino acid phenylalanine. The mode of inheritance for PKU is autosomal recessive. Nearly all cases are caused by mutations in the gene encoding PAH and its deficiency, which has been mapped to chromosome 12. More than 500 have been identified, the most common mutation in The Czech Republic and in The Europe is R408W. The hepatic enzyme phenylalanine hydroxylase (PAH) catalyzes the conversion of phenylalanine to tyrosine. Complete enzyme deficiency results in classical PKU, in which serum phenylalanine concentration exceeds 20 mg/dL (1200 micromol/L) and levels are elevated in the urine. Residual enzyme activity causes mild PKU (phenylalanine concentration 10 to 20 mg/dL, 600 to 1200 micromol/L) and mild hyperphenylalanemia (mild HPA, phenylalanine concentration 2.5 to 10 mg/dL, 150 to 600 micromol/L). Tyrosine concentration is normal or nearly normal. Tetrahydrobiopterin (BH4) is a cofactor required for PAH activity. Defects in BH4 metabolism account for approximately 1-2 percent of patients with elevated phenylalanine levels. In untreated patients, the hallmark of the disease is mental retardation and other neurological and psychical symptoms including epilepsy, but because of widespread neonatal screening, overt clinical manifestations of PKU are rare. Light pigmentation is common, and patients may have an eczematous rash. The body and urine may have a specific "mousy" odor due to the increased concentration of the metabolite phenylacetic acid. Diagnosis of PKU is based upon the finding of an elevated serum concentration of phenylalanine together with low to low-normal tyrosine concentration. The most useful laboratory method for newborn screening is tandem mass spectrometry. Full-area newborn screening in the Czech country was established 1st January in 1975. Molecular analysis can be used to demonstrate mutations at the PAH locus in peripheral blood leukocytes or for carrier detection or prenatal diagnosis in families in whom the mutation is known. Patients with both classic and mild phenylketonuria require lifelong a dietary restriction of phenylalanine. This requires the use of medical foods

including phenylalanine-free protein substitutes (amino acid mixtures). This restrictive diet is associated with a risk of nutritional deficiencies and represents a burden for the patients and their families. Treatment should be initiated as soon as possible, usually before one week of age and blood concentrations of phenylalanine should be monitored frequently, especially during infancy. BH4 deficiency should be excluded before the treatment. Diagnosis of BH4 deficiency is made by measurement of elevated concentrations of biopterin or neopterin in blood, urine, or cerebrospinal fluid and DHPR in a dry drop of blood. Neurotransmitter metabolites also are measured in cerebrospinal fluid. Some types of BH4 deficiency is treated with a diet low in phenylalanine and also supplementation with a biologically active synthetic form of BH4 and the neurotransmitter precursors L-dopa, carbidopa and selegilin. Folinic acid supplementation is given in DHPR deficiency. Elevated serum phenylalanine concentration during early pregnancy in a mother with PKU or hyperphenylalanemia can result in phenylalanine embryopathy includes intrauterine growth restriction, mental retardation, microcephaly, and malformations, mainly congenital heart defects. The risk of abnormalities depends upon the maternal blood phenylalanine concentration and is independent from the fetal genotype (heterozygosity or homozygosity for PKU) – that´s why women should reach for low maternal phenylalanine concentrations by dietary restriction of phenylalanine ideally at least three months before conception and keep it up during pregnancy <4 mg/dL (240 micromol/L).