Phenylketonuria
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Phenylketonuria (PKU) is an inborn error of amino acid metabolism in which a deficiency of the hepatic enzyme phenylalanine hydroxylase (PAH) causes a decreased hydroxylation of phenylalanine into tyrosine. Left untreated, PKU results in serious mental retardation. However, PKU can be detected and treated in neonates before damage to the central nervous system has occurred to a large degree. The treatment is based on a diet restricted in natural protein and supplying the patient with a tyrosine-enriched amino acid mixture devoid of phenylalanine resulting in a more or less normal total protein intake. This treatment has contributed considerably to the improvement of the intellectual outcome of these patients, but even early treated PKU patients still encounter some abnormalities in the intellectual, neuropsychologic and psychosocial development. As the aim of today should not only be to prevent mental retardation but also to enable patients with PKU to develop as a normal and happy child into a normal adult with a normal life, many questions need to be answered.

In this thesis, attention is paid to growth which may be impaired due to the severe dietary Phe restriction; the possibility of distinction between patients with differences in PAH enzyme activity by direct measurement of the in-vivo phenylalanine hydroxylation; plasma Phe and Tyr concentrations in response to different distributions of the daily intake of PKU patients; and some issues concerning pregnancy and PKU.

In the introduction (chapter 1) some aspects of PKU are outlined which present either some general background information or are very relevant to the issues discussed in PKU today. Such issues are the lack of clearness on the definition of the term PKU, and the lack of consensus on the method used to differentiate between patients with different levels of PAH deficiency. It is argued that dietary restriction is the sole treatment of choice with - on the one hand - large positive effects, but - on the other hand, no complete normal intellectual, neuropsychologic and psychosocial development. Therefore, various issues still need to be solved to optimize the treatment of PKU individuals from the unborn child to the adult and the woman with PKU who carries a child herself.
Summary

In chapter 2, growth and the effect of different degrees of dietary restriction were studied in Dutch patients with early and continuously treated PKU. In these studies, it was found that growth retardation occurs during the first three years of life, but that no relationship exists between different degrees of the strictness of dietary treatment and the previously described growth retardation. The last finding is important because the targetted phenylalanine concentrations have been decreased during the recent years.

In chapter 3, the in-vivo hydroxylation of phenylalanine into tyrosine was investigated using stable isotopically labelled phenylalanine and tyrosine. By this method, theoretically, the hydroxylation rate of phenylalanine can be measured without causing a substantial increase of the plasma phenylalanine concentration. In this thesis it was shown that continuously treated PKU patients have decreased in-vivo phenylalanine hydroxylation rates. This finding is in contrast with the results of other studies. Further studies are needed to investigate the usefulness of this technique in order to select between patients with differences in the degree of the PAH deficiency at an early age.

In chapter 4 and 5, the daily fluctuations of both plasma phenylalanine and tyrosine were studied in relation to different distributions of the daily individually tailored dietary natural protein intake.

From the studies concerning the daily fluctuations of phenylalanine in plasma (chapter 4) it was concluded that the nutritional condition (fasting/postprandial) and the exact time of the day the blood sampling is performed are not important in the evaluation of the phenylalanine intake, and that unequal distributions of the daily phenylalanine allowance are justified in PKU patients on an occasional base provided that the patient is in good clinical condition, adjusted adequately to the diet, and given that the daily allowance is not exceeded. Regarding these two conclusions, it should be stressed that only patients older than 1 year of age were studied and that further studies are necessary for patients younger than 1 year of age.
Phenylketonuria: implications of some biochemical and clinical findings

The studies of the daily fluctuations of tyrosine concentrations in plasma (chapter 5) showed that these fluctuations can be large resulting in very high tyrosine concentrations. These studies further showed that even patients with an even distribution of their protein intake may encounter both too low and too high tyrosine concentrations at the same day. It could, therefore, be concluded that a single blood sample either taken in the overnight fasting or postprandial condition is insufficient to detect a possible tyrosine deficiency and that a combination of a pre- and postprandial blood sample on the same day may be more effective. Second, it could be concluded that strict control of plasma tyrosine is necessary when extra tyrosine supplementation is considered in addition to the tyrosine-enriched amino acid mixtures.

In chapter 6, different aspects concerning PKU and pregnancy were discussed, including both the fetal condition of the PKU patient and that of the offspring of a female patient with PKU (maternal PKU). It was shown that in PKU children the risk of congenital heart disease and low birth weight may be increased. In this chapter information is also given on reference values of amino acid concentrations in maternal blood which are necessary for the treatment of maternal PKU.

In the general discussion (chapter 7) the results of chapter 2 to 6 are discussed. Attention is focussed on the need of a method to distinguish between patients with different PAH enzyme activity and the problems related to the method which is most often used (phenylalanine tolerance at 5 years of age according to Güttler). Further, difficulties in the treatment of maternal PKU are discussed. The chapter ends with a short enumeration of aspects of treatment which deserve special attention to optimize the intellectual and neuropsychologic outcome and to decrease the psychosocial burdensome of the treatment.