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Successful treatment of phenylketonuria with tetrahydrobiopterin

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Sir: Worldwide newborn screening for phenylketonuria (PKU) and early dietary treatment of patients with impairment of the enzyme phenylalanine hydroxylase has resulted in prevention of mental retardation in more than 3000 patients [3]. However, a small number of patients with increased blood phenylalanine (Phe) levels have a defect of the coenzyme tetrahydrobiopterin (BH_4) which leads to hyperphenylalaninaemia (HPA) and neurotransmitter deficiency. They are treated by BH_4 and neurotransmitter supplementation [1]. Up to now, no patient with a defect in the apoenzyme was found who can simply be treated by supplementation of BH_4. One of our PKU patients responsive to BH_4 supplementation was found in the newborn screening programme with blood Phe levels of 96 μmol/l (reference range 36–108 μmol/l) and at 14 days of age of 885 μmol/l. BH_4 loading (20 mg/kg body weight) resulted in a decrease of blood Phe to 67 μmol/l 8 h post-loading. Under normal feeding with a breast milk adapted formula, plasma Phe levels rose again to 934 μmol/l. With a daily supplementation of 10 mg/kg of BH_4 (Dr. Schircks Laboratories, Jona, Switzerland), blood Phe levels dropped again and remained between 84 and 222 μmol/l. Surprisingly, there was no BH_4 coenzyme deficiency (normal values for neopterin and biopterin in urine, normal dihydropteridine reductase activity in red blood cells, and normal neurotransmitters and pterins in cerebrospinal fluid). However, mutation analysis of the phenylalanine hydroxylase gene revealed the two mutations IVS10G^{-11}A in intron 10 and E390G in exon 11. The first one creates a zero activity of the enzyme, the second one is a missense mutation, together resulting in a phenotype with mild PKU [4]. The patient is now at 10 months of age on 10 mg BH_4/kg per day and developing normally. We speculate that there may be more mutations resulting in a K_m-variant of the phenylalanine hydroxylase enzyme in which enhancement of the residual activity can be achieved by supplementation of BH_4 as recently also found in hyperphenylalaninaemic patients in Japan [2]. Our observation strongly emphasises the necessity of the BH_4 loading test in the newborn period and further DNA mutation analysis in hyperphenylalaninaemic patients responsive to BH_4 supplementation. BH_4 supplementation instead of a low Phe dietary treatment may be possible in at least some patients with PKU or mild PKU. In these cases, treatment compliance with coenzyme substitution may be much better in adulthood.

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