Plasma phenylalanine is associated with decreased serum ubiquinone-10 concentrations in phenylketonuria

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Summary: Decreased serum ubiquinone-10 concentrations is a common condition in patients with phenylketonuria (PKU) under dietary treatment. Our aim was to investigate the implication of the metabolic abnormalities of PKU (low concentrations of tyrosine and high concentrations of phenylalanine) and the effect of treatment with phenylalanine-restricted diets in decreased ubiquinone-10 concentrations in PKU patients. We studied 30 PKU patients (age range 5 months to 35 years; median age 7 years) under dietary treatment. Correlation between plasma tyrosine or phenylalanine and serum ubiquinone-10 concentrations was investigated. Daily cholesterol intake was calculated from the data obtained through a dietary questionnaire. The index of dietary control (IDC) was calculated as the average of the medians of plasma phenylalanine concentrations obtained every 6 months in the metabolic control of patients. Negative correlations were observed between serum ubiquinone and the IDC ($r=-0.46; p<0.01$) in PKU patients. No correlation was observed between tyrosine or daily cholesterol intake and serum ubiquinone concentrations. After adjustment for daily cholesterol intake by multiple linear regression analysis, for each 113 units of increase in IDC values serum ubiquinone decreased 0.1 μmol/L. According to our results, the main factor associated with the decreased serum ubiquinone concentrations was high plasma phenylalanine values. Although daily cholesterol intake seems to be associated with ubiquinone concentrations, it may not be relevant if we take into account the low intake of cholesterol in treated PKU patients.
Phenylketonuria (PKU; McKusick 261600) is an inborn error of phenylalanine metabolism resulting from deficient activity of L-phenylalanine 4-monooxygenase (EC 1.14.16.1), the enzyme that catalyses the synthesis of tyrosine from phenylalanine (Scrivener et al 1995).

In a previous report, we reported decreased serum ubiquinone-10 concentrations in PKU patients under phenylalanine-restricted diet (Artuch et al 1999). However, we could not determine the factors associated with this mild deficiency. Ubiquinone-10 is a lipid that has been implicated in several biological functions. It has an important role in energy transduction in mitochondria. Moreover, in its reduced form (ubiquinol) it protects molecules from peroxidative damage (Ernster and Dallner 1995; Stocker et al 1991). Ubiquinone-10 is synthesized through two metabolic pathways: the quinone moiety of ubiquinone is synthesized predominantly from tyrosine, while the polypropyl side chain is synthesized from acetyl-CoA through the mevalonate pathway common for cholesterol synthesis (Ernster and Dallner 1995). Both metabolic processes are necessary for syntheses of ubiquinone. Moreover, serum ubiquinone concentration depends on dietary sources, which may contribute up to 25% of total ubiquinone (Weber et al 1997).

There are three main factors probably involved in the decreased serum ubiquinone-10 concentrations in PKU patients. The first is a deficient intake: foods such as poultry and meat that are restricted for PKU patients may be critical for the maintenance of optimal serum ubiquinone-10 concentration (Weber et al 1997). Secondly, a tyrosine deficiency would decrease ubiquinone-10 biosynthesis. Thirdly, high phenylalanine concentrations cause inhibition of the rate-limiting enzymes of cholesterogenesis (especially 3-hydroxy-3-methylglutaryl-CoA reductase), demonstrated in experimental hyperphenylalaninaemia (Castillo et al 1988; Shefer et al 2000).

Our aim was to investigate the implication of the metabolic abnormalities of PKU (low concentrations of tyrosine and high concentrations of phenylalanine) and the effect of treatment with a low-protein diet in the ubiquinone-10 decrement observed in PKU patients.

**SUBJECTS AND METHODS**

We studied 30 PKU patients (age range 5 months to 35 years; median age 7 years) periodically monitored in our hospital (a reference centre for PKU in Catalonia) over two years (1999–2000). Nine of these 30 patients have already been included in a previous study (Artuch et al 1999). All patients were on a phenylalanine-restricted diet supplemented with a tyrosine-enriched amino acid mixture (Analog XP in infancy, Maxamid XP in childhood, and Maxamum XP in adolescence and adulthood; Scientific Hospital Supplies, Barcelona, Spain). For this study we selected PKU patients with good metabolic control (index of dietary control (IDC) ranging between 205 and 643 µmol/L; median 341) in order to try to establish the causes of decreased ubiquinone in a homogeneous PKU population.

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