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The challenge of long-term tetrahydrobiopterin (BH_4) therapy in phenylketonuria: Effects on metabolic control, nutritional habits and nutrient supply

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ABSTRACT

Background and aims: BH_4-sensitive phenylketonuria (PKU) patients relax their phenylalanine (Phe) restricted diet due to increased Phe tolerance, while keeping dried blood Phe concentrations with in the therapeutic range. We aimed to investigate metabolic control, eating habits and nutrient supply under long-term BH_4-therapy.
Patients and methods: Retrospective analysis of mean dried blood Phe concentrations and their variability, food and nutrient intake in BH_4-sensitive patients (n = 8, 3f, age 6.0–16.6 y) under classical dietary treatment for one year and during the three years after initiation of BH_4.
Results: Phe concentrations of BH_4-sensitve PKU patients remained within therapeutic range throughout the observation period, independent of therapeutic regime. Under BH_4, Phe tolerance increased significantly (493.2 ± 161.8 mg/d under classical diet vs 2021.93 ± 897.4 mg/d two years under BH_4; P = 0.004). Variability of Phe concentrations remained unchanged (mean SD; P = 1.000). Patients adjust their food choice and significantly increased their intake of cereals, potatoes, dairy products and meat (P = 0.019, P = 0.016, P = 0.016 and P = 0.016, respectively). Under diet changes after implementation of BH_4 a drop in micronutrient intake (vitamin D, folic acid, iron, calcium, iodine) could be revealed (P = 0.005, P < 0.001, P = 0.004, P = 0.001, P = 0.003, respectively).
Conclusions: BH_4-sensitive PKU patients can achieve good metabolic control under an adjuvant BH_4- or a BH_4 monotherapy. The liberalized diet under BH_4 seems to jeopardize the quality of patients' nutrition, and these patients require close follow-up and special nutrition education to minimize the risk for imbalanced diet and nutrient deficiencies.

1. Introduction

Since approval of sapropterindihydrochlorid (BH_4) for the treatment of BH_4-sensitive phenylketonuria (PKU, OMIM 261600), a large number of patients switched from classical dietary treatment (phenylalanine (Phe) restricted diet and Phe-free amino acid supplements enriched with micronutrients) to an additional BH_4 supplementation [1]. BH_4 therapy usually allows increase of daily Phe consumption by a factor of 2–3, still keeping Phe concentrations in dried blood within the therapeutic range [2]. Some BH_4-sensitive PKU patients can entirely stop dietary treatment and no longer need any amino acid supplement (AAM) [2,3,4]. As a consequence, quality of life, therapy adherence and thus, long-term metabolic control and outcome of these patients might be improved [1,5]. Moreover, there is some evidence for a stabilization of Phe concentrations under BH_4 therapy [6,7]. This is of

Abbreviations: AAM, amino acid mixture; BH_4, tetrahydrobiopterin; Phe, phenylalanine; PKU, phenylketonuria.

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importance as the stability of Phe concentrations in the organism seems to have a relevant influence on long-term cognitive outcome [6,8,9,10]. Higher Phe fluctuations are associated with cognitive deficits, especially with a negative impact on working memory, inhibitory control and executive strategic processing [9].

Switching from a Phe restricted diet to a relaxed or even free diet under BH_4 supply is a challenge. Due to the increased Phe tolerance, patients are allowed to extend their choice of natural food. Initially, they maintain some of their customary eating patterns such as a restricted consumption of food with high protein content e.g. dairy products, fish or meat. At the same time, they partly adopt eating habits of the general population. As a consequence, fruit and vegetable consumption markedly decreases, while the supply of potatoes, pasta and rice exceeds the average intake of the healthy peers [2]. Such an imbalanced nutrition bears a high risk for an insufficient micronutrient intake [2, 11] and may result in impaired physical and neurological development [12,13,14]. Changing eating habits, indeed, is difficult, as food preferences and aversions primarily develop during the first years of life resulting in stable and almost unchangeable eating patterns [15].

The study presented here aimed to evaluate metabolic control, including variability of blood Phe, as well as food and nutrient intake in BH_4-sensitive PKU patients under long-term BH_4 therapy.

2. Patients and methods

2.1. Patients

A retrospective analysis of metabolic control comprising variations of Phe concentrations as well as food and nutrient intake over a period of four years (one year prior BH_4 and three years under BH_4 treatment) in eight BH_4-sensitive PKU patients (3f/5 m) was performed. All patients proved to be BH_4-sensitive by a six week prolonged BH_4-responsiveness test, as previously described [5]. All included PKU patients were diagnosed by newborn screening and early and continuously treated by a Phe restricted diet with essential amino acid as well as micronutrient supply by AAM until the start of BH_4. They followed the BH_4 therapy at least for three years. Patients received individual diet counseling at each clinical visit, at least four times a year.

The study was approved by the University of Leipzig's ethics committee (registration-number 440-12-17122012) and registered at DRKS, the International Clinical Trials Registry Platform (DRKS00004942).

3. Methods

3.1. Assessment of dried blood Phe concentrations

Dried blood Phe concentrations were regularly assessed according to the current recommendations for treatment of PKU for the German speaking countries [16]. Phe concentrations in dried blood were determined by liquid chromatography/tandem mass spectrometry (LC–MS/MS), as previously described [17].

3.2. Assessment of food and nutrient intake

Information about food consumption and nutrient intake (Phe, energy, macro- and micronutrients: iron, iodine, calcium, zinc, vitamin D, C, B1, B2, B6, B12 and folic acid) was gathered from detailed three-day dietary records. Food choice and mean nutrient intake of BH_4-sensitive patients were evaluated before (under classical PKU diet) and after three months and two years of BH_4-therapy.

All ingested food was allocated to food groups as previously described [2] and shown in Fig. 1. Nutritional analysis was conducted using the Food and Control Management System "Diät 2000" based on the updated version of the Bundeslebensmittelschlüssel [18]. Additional information on AAM, low protein food as well as other processed food provided by the manufacturers was added to the database.

Mean nutrient intake of BH_4-sensitive patients under BH_4 therapy was compared to the current recommendations for nutrient intake [19]. In addition, mean nutrient as well as food intake were compared to data from a cohort of age-matched healthy German children [20].

3.3. Statistics

All procedures were performed using SPSS for Windows 20 (SPSS Inc., Chicago, Illinois).

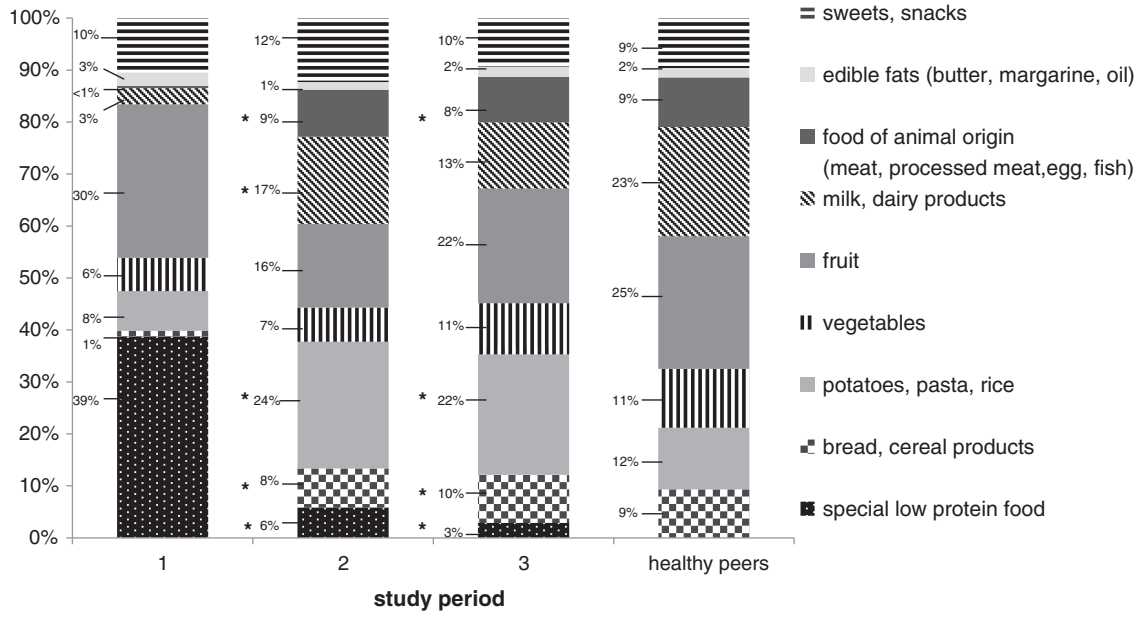

Fig. 1. Food consumption of BH_4-sensitive patients under Phe restricted diet (bar 1) compared to BH_4 therapy three months and two years after its introduction (middle bars 2 and 3) compared to age-matched healthy German children (right bar). Shown are the shares of food groups (%) of total food consumption (*significant differences in BH_4-sensitive patients under Phe restricted diet compared to BH_4 therapy:bread: study period 1 vs. 2 $P = 0.014$ and 1 vs 3 $P = 0.019$; potatoes, pasta rice 1 vs 2 $P = 0.008$ and 1 vs 3 $P = 0.016$; milk/dairy products: 1 vs 2 $P = 0.016$; food of animal origin (meat, processed meat, fish, egg): 1 vs 2 $P = 0.008$ and 1 vs 3 $P = 0.016$; special low protein products: 1 vs 2 $P = 0.008$ and 1 vs 3 $P = 0.016$).