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Risk factors for developing mineral bone disease in phenylketonuric patients

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ABSTRACT

There is a compromised bone mass in phenylketonuria patients compared with normal population, but the mechanisms responsible are still a matter of investigation. In addition, tetrahydrobiopterin therapy is a new option for a significant proportion of these patients and the prevalence of mineral bone disease (MBD) in these patients is unknown.

We conducted a cross-sectional observational study including 43 phenylketonuric patients. Bone densitometry, nutritional assessment, physical activity questionnaire, biochemical parameters, and molecular study were performed in all patients. Patients were stratified by phenotype, age and type of treatment.

The MBD prevalence in phenylketonuria was 14%. Osteopenic and osteoporotic ($n = 6$ patients) had an average daily natural protein intake significantly lower than the remaining ($n = 37$) patients with PKU (14.33 ± 8.95 g vs 21.25 ± 20.85 g). Besides, a lower body mass index was found. There were no statistical differences in physical activity level, calcium, phosphorus and fat intake, and in phenylalanine, vitamin D, paratohormone, docosahexaenoic and eicosapentaenoic acid blood levels. Mutational spectrum was found in up to 30 different *PAH* genotypes and no relationship was established among genotype and development of MBD. None of the twelve phenylketonuric patients treated with tetrahydrobiopterin (27.9%), for an average of 7.1 years, developed MBD. Natural protein intake and blood levels of eicosapentaenoic acid were significantly higher while calcium intake was lower in these patients.

This study shows that the decrease in natural protein intake can play an important role in MBD development in phenylketonuric patients. Therapy with tetrahydrobiopterin allows a more relaxed protein diet, which is associated with better bone mass.

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1. Introduction

Phenylketonuria (PKU, OMIM 261600) is an autosomal recessive inborn error of metabolism due to mutations in the phenylalanine hydroxylase (PAH) gene (NM_000277); this enzyme deficiency leads to elevated levels of phenylalanine (Phe) in the blood and in other tissues including the brain, as well as to corresponding neurotoxic effects. The treatment of PAH deficiency is based on the dietary restriction of phenylalanine and therefore, natural proteins. Synthetic protein supplementation with special formula is needed to prevent malnutrition. In those patients who respond positively to BH4, administration of the cofactor increases the residual enzymatic activity, allowing liberalization of the diet [1–4].

PKU is usually detected by newborn screening, enabling an early diagnosis and treatment, thus preventing the development of profound and irreversible neurological sequelae. The prevention of mental retardation and other complications typical of the disease highlights less-known aspects of it, which determine the quality of life, including mineral bone disease (MBD) [5–8].

MBD is characterized by reduced bone strength, leading to an increased risk of fracture. Bone strength depends on the density and quality of bone. Bone mineral density (BMD) is determined from the peak

Abbreviations: BH4, 6R-5,6,7,8-tetrahydrobiopterin; BMI, body mass index; DEXA, bone densitometry; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MBD, mineral bone disease; PHE, phenylalanine; PTH, parathyroid hormone; PKU, phenylketonuria; WHO, World Health Organization.

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bone mass and the amount of bone loss. Bone quality, however, refers to the macro- and micro-architecture, bone turnover, size, accumulated damage (e.g., microfractures) and mineralization [9]. MBD is asymptomatic until a fracture occurs.

The pathophysiology of MBD is characterized by two factors; on one hand, the decrease in bone mass in 80% of the cases is genetically determined, and the remaining 20% is due to external factors such as sedentary lifestyle or low calcium diet [10,11]. The other factor is the deterioration of bone microarchitecture, which occurs when bone resorption exceeds formation. In some PKU patients there is an increase in circulating osteoclast precursors [12], which increases bone resorption and favors the development of MBD.

The current incidence and etiology of MBD in PKU patients is unknown. Several theories have been proposed, such as dietary deficiencies due to the protein restriction implicit in treating the disease, irregular diet compliance, which causes fluctuating blood Phe levels [6], sedentary and genetic factors linked to the disease itself that can determine changes in bone remodeling [7,8].

The definition–classification of osteoporosis by the World Health Organization (WHO) is used to identify patients who develop this complication. This definition is based on the measurement of BMD by bone densitometry (DEXA).

The aim of our study was to determine the incidence of MBD in a group of patients with PKU and to analyze potential risk factors involved in its appearance.

2. Subjects and methods

The study protocol was approved by the Ethics Committee of the Hospital Universitario de Santiago. All patients or their parents (children under 16 years) were properly informed and signed an informed consent to enter the study.

2.1. Study design

A cross-sectional observational study was conducted from October 2010 to December 2011. We included all patients over 7 years old, diagnosed with PKU, followed-up in our reference center for congenital metabolic diseases, in Galicia, north-west Spain. We included both patients diagnosed by newborn screening as well as those diagnosed later. Those with benign hyperphenylalaninemia (Phe <360 μmol/L) were excluded, as well as those cases in which informed consent was not signed by parents and/or patients.

2.2. Data collection

The variables collected from each patient were: age, sex, anthropometric data, nutritional survey by collecting intake for a week, survey on physical activity, levels of Phe at diagnosis, phenotype (mild hyper-Phe 120–600 μmol/L; mild PKU 600–900 μmol/L; moderate PKU 900–1200 μmol/L; classic > 1200 μmol/L), blood chemistry (Phe, renal and liver function, electrolytes, levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 25-hydroxy vitamin D (25(OH)D), 1–25 hydroxy vitamin D (1-25(OH)2D), parathyroid hormone (PTH), and bone mineral density. All biochemical measurements were obtained from fasting morning plasma samples.

2.3. Methods

Tandem mass-spectrometry was used for measuring the Phe levels from dried blood spots. Proteins, urea, creatinine, transaminases, calcium, phosphate, magnesium and total alkaline phosphatase were determined by standard procedures with the Advia 2400 Analyser (Siemens Diagnostic Systems, Germany). PTH, 25 (OH) D and 1–25 (OH) 2D were determined by a fully automated electrochemiluminescence system (Roche Diagnostic GmbH, Mannheim, Germany). Plasma lipids were extracted from the blood according to the method developed by Folch et al. [13]. Phospholipids were subsequently isolated by thin-layer chromatography (TLC Silica gel 60, 20×20 cm, Merck, Spain). First, a mixture of heptane, diisopropyl ether, and acetic acid (7/3/0.2 v/v) was employed as the eluent and then heptane as the second eluent. After being removed from the silica matrix, the phospholipids were transmethylated according to Lepage and Roy [14] using tridecanoic acid as the internal standard. The fatty acid methyl esters were separated on a Hewlett Packard GC 5890 gas chromatograph using a flame-ionization detector on a capillary column SP 2330 (30 m× 0.25 mm, 0.20 μm) (Supelco, Bellefonte, PA, USA), with hydrogen as the carrier gas. The results were expressed as mg fatty acid/g total fatty acids in PLs.

The calculation of the nutritional diet was assessed, by survey of the intake by a week through self-designed software: www.odimet.es.

Regular physical activity of each patient was assessed according to the results obtained after completing the GPAQ (Global Physical Activity Questionnaire), and classified into three levels: low (if score<6), intermediate (score 6–10), and high (score>10) [15].

BMD was measured by bone densitometry of lumbar spine (L2, L3 and L4) and proximal femur by dual-energy X-ray absorptiometry (DEXA LUNAR DPX, General Electric). For the adult population, using the normal database Hologic NHANES III, the presence of MBD was defined following the WHO criteria using the t-score: number of standard deviations compared to a reference normal young population; a t-score<−2.5 was interpreted as osteoporosis, and a t-score between −2.5 and −1 as osteopenia. The z-score, comparing BMD with a population of similar age and sex, was used in children under 20 years, using the data published by Zanchetta et al. [16], as reference values.

2.4. Statistical analysis

We used the statistical program SPSS®, version 20.0 (SPSS Inc., Chicago, Illinois, USA). The descriptive analysis results are expressed both in absolute units and as percentages. When appropriate, data are expressed as mean ± standard deviation. A $p<0.05$ was considered significant. Comparison of qualitative and quantitative discrete variables was performed using Chi-square and Fisher exact test was determined by the adjustment of variables to normal. Comparison of the means of quantitative variables was done using the Student-t test if they followed normal distribution, and using the Mann–Whitney U test if not.

3. Results

A total of 43 PKU patients were included (41.9% male, mean age 17.6 years, range: 7.1–41 years), of whom 28 (65.1%) were under 20 years. Almost two-thirds of the patients (27, 62.8%) were diagnosed with classical PKU, 9 (20.9%) with moderate PKU, and 7 (16.3%) with mild PKU. Fourteen patients were diagnosed late by clinical symptoms (32.6%). Twelve patients (28%) were treated with BH4, of which one was with classic PKU, 6 were with mild PKU and 5 with moderate PKU.

MBD was detected, according to the BMD, in 6 patients (14%), 3 females and 3 males, with a mean age of 24.17 ± 14.55 years (range 7–41 years). Two of them were diagnosed with moderate PKU, the rest with classical PKU. Of these, 4 had osteopenia and 2 had osteoporosis (Table 1). The PKU was diagnosed late more often in the patient group with MBD (66.7% vs 27%, $p=0.077$).

Mutational spectrum was found in up to 30 different genotypes, showing great genetic heterogeneity, most of them falling on the category of missense types. There is o relation between the genetic study and the development or not of MDB in the patients (data not shown of all mutations). There are mutations with a null or very low PAH activity in vitro in both groups.

No family history consists of osteopenia/osteoporosis in any patient with BMD.

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