PHENYLKETONURIA - THE NUTRITIONAL INTERVENTION IN PORTUGAL

Fenilcetonuria - La nutrición Intervención en Portugal

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RESUMEN

Introducción: Fenilcetonuria, también conocida como PKU está clasificada como un defecto congénito del metabolismo o enfermedad metabólica. Es un trastorno hereditario, autosómico recesivo, que se produce por mutaciones en el gen que codifica la actividad de la enzima fenilalanina hidroxilasa (PAH). Objetivo: recopilar recomendaciones para terapia nutricional de PKU, tomando en consideración las pruebas y el consenso científico publicados. Metodología: La estrategia de búsqueda utilizada para esta revisión sistemática basada en prueba científica se basó en la búsqueda de palabras clave en las siguientes bases de datos electrónicas: Academic Search Complete (EBSCO); RCAAP; Annual Reviews; Biomed Central; Current Contents (ISI); Elsevier - Science Direct; Highwire Press; Wiley; Pubmed; Scopus, Science, LILACS and Springer. La búsqueda en estas bases de datos se llevó a cabo entre diciembre de 2014 y septiembre de 2015. Resultados: A lo largo del estudio fue posible identificar importantes desafíos nutricionales, en particular: Mantener los niveles de Phe en los límites requeridos para cada individuo; Conseguir los niveles de energía y nutricionales de esos pacientes; Educación nutricional permanente; Prevención del sobrepeso / obesidad; Prevención de retrasos en el crecimiento; Monitorización de los niveles de Phe / TYR en sangre para una adecuación constante de la dieta; la composición de las tablas de alimentos en Portugal no incluyen los valores de proteínas necesarios, faltando la cuantificación por año. Conclusión: Este estudio muestra la importancia del tratamiento de la PKU y su diagnóstico temprano como factores claves para que pacientes con esta enfermedad puedan obtener una calidad de vida similar a la de individuos sanos. La terapia nutricional es muy rígida y debería mantenerse de por vida. Por ello es importante proporcionar a estos individuos y sus familias educación nutricional.

Palabras claves: Fenilcetonuria, terapia nutricional, fenilalanina hidroxilasa.

ABSTRACT

Introduction: Phenylketonuria, also known as PKU is classified as an inborn error of metabolism or a metabolic disease.It is an inherited disease, autosomal recessive, occurring by mutations in the gene that encodes the activity of the enzyme phenylalanine hydroxylase (PAH). Objetive : compile the recommendations for nutritional therapy in PKU, taking into account the evidence and published scientific consensus. Methodology: The search strategy used for this systematic review based as scientific evidence was based on the search for keywords in the following electronic databases: Academic Search Complete (EBSCO); RCAAP; Annual Reviews; Biomed Central; Current Contents (ISI); Elsevier - Science Direct; Highwire Press; Wiley; Pubmed; Scopus, Science, LILACS and Springer. The research in this databases was held up between December 2014 and September 2015. Results: Throughout this state of the art was possible to identify the major nutritional challenges, in particular: Keeping the Phe levels within the limits required for each individual; Achieving the energy and nutritional needs of these patients; Lifelong nutrition education; Preventing overweight / obesity; Prevent delays in growth; Monitoring Phe / TYR blood levels to constant adequacy of the diet; The food composition tables in Portugal do not include the necessary protein values, lack of quantification per year. Conclusion: This state of art shows the importance of PKU treatment and early diagnosis as key factors for patients with this disease, in order to obtain quality of life, similar to healthy individuals. The nutritional therapy is very rigid and should be maintained throughout lifetime. So is very importance to provide to this individuals and their families food education.

Key word: Phenylketonuria, nutritional therapy, phenylalanine hydroxylase.

INTRODUCTION

Phenylketonuria, also known as PKU is classified as an inborn error of metabolism or a metabolic disease [(1)]. It was first identified by neonatal screening [(2)].

It is an inherited disease, autosomal recessive, occurring by mutations in the gene that encodes the activity of the enzyme phenylalanine hydroxylase (PAH) [(3)].

PAH is the enzyme responsible for converting phenylalanine (Phe) tyrosine (TYR) by (6R)-L-erythro-5, 6, 7, 8-tetrahydrobiopterin (BH4) [(4)].

In this pathology, Phe, essential amino acid (aa), that is found in protein foods, is not metabolized in TYR, due to deficiency or inactivity of PAH or diidropteridina redutase

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(DHPR) [5].

PKU results from the accumulation of Phe in the blood, hyperphenylalaninemia (HFA), on various classifications, according to the degree of inactivity of PAH, and was first described in 1934 by Asbörn Folling [6].

Untreated PKU individuals have severe mental retardation, with episodes of seizures and behavioral disorders [7].

A deficiency in PAH is common in Caucasians with incidence rates in Europe 1/10000 births, existing countries where this is greater, namely Ireland and Turkey [2].

The treatment of PKU goes through nutritional therapy with protein restriction in Phe. However, the diet must be delineated in order to provide the individual with a sufficient amount of this essential aa for their development, growth and state of health are not compromised.

The therapies developed to date, either combined or isolated, undergo nutritional treatment, use of Phe food products, cofactors pharmacological administration, BH4, and genetic mediation.

International guidelines for the treatment of PKU still have some gaps, because the results obtained by the various therapies are inconclusive, since its longitudinal follow-up is not yet complete. However, this state of the art has been prepared in order to compile the recommendations for nutritional therapy in PKU, taking into account the evidence and published scientific consensus.

The areas of research in the treatment of PKU include the choice of modified food products, integration of adjuvant therapies, treatment during pregnancy, nutritional monitoring and biomarkers, preventing nutritional deficiencies, access to health care and build therapeutic strategies [8].

METHODOLOGY

The search strategy used for this systematic review based as scientific evidence was based on the search for keywords in the following electronic databases: Academic Search Complete (EBSCO); RCAAP; Annual Reviews; Biomed Central; Current Contents (ISI); Elsevier - Science Direct; Highwire Press; Wiley; Pubmed; Scopus, Science, LILACS and Springer.

The research in this databases was held up between December 2014 and September 2015.

The identification and selection of the studies to be included in this review where based in the guidance issues, including participants; the phenomenon of interest to create a connection to define a set of synonyms and related terms for intersection that would lead to the search string (keyword).

In addition, a manual search in the literature from clinical trials was conducted, systematic reviews and meta-analyzes were included to search unidentified items in the database.

Physiopathology

The PKU is a metabolic disease, an autosomal recessive genetic linked to chromosome 12q23.1, the gene called PAH11. Currently, they have been identified over 800 mutations in the PAH gene [3].

PAH is a liver enzyme that catalyzes the hydroxylation of Phe in TYR. When this reaction is deficient, TYR assumes, by its absence, that the same character Phe, becoming a critical aa for these individuals [1].

The PKU patients exhibiting deficiency in PAH or in the enzyme DHPR. Therefore, Phe is not metabolised to TYR, leading inevitably to the increased of Phe concentration

in the blood. It is necessary the recruitment of secondary pathways that are able to metabolize a small fraction of the accumulated substrate, yielding phenylpyruvic acid, phenyllactic acid, phenylacetic acid, among others, which are excreted in large quantities in urine [7].

The PKU untreated individuals have disturbances in brain development, with neurological symptoms such as microcephaly, epilepsy and mental retardation [9].

The various classifications and types of PKU are discussed by several authors. However in Camp et al., 2014, to standardize the terminology used, was created a qualification to the PKU´s subtype.

The PKU subtypes are: classical PKU the more severe, characterized by blood levels of Phe> 20mg / dL or> 1200µmol / l; moderate PKU Phe blood values between 15-20mg / or 900-1200µmol gl / l; mild PKU Phe concentrations of between 6-15mg / dl or 360-900µmol / l and HFA Phe values between 2-6mg / dl or 120-360µmol / l [10].

DIAGNOSIS

The use of neonatal screening allows almost all cases in PAH deficiency were diagnosed and subsequently quantitatively measured for the degree of HFA [2].

The purpose of diagnosing PKU early is to prevent mental deterioration and other manifestations of the pathology.

Diagnostic tests for PKU are based on detection of blood levels of Phe and / or its metabolites in urine. Sorting through the urine metabolites is inadequate for early diagnosis, as changes in urine only emerge after the changes identified in the blood [12].

The most widely used neonatal test in Portugal, to qualitatively diagnose PKU, is the blood test Guthrie or also called the Foot Test [13]. It is a simple laboratory test whose card in blood collection is performed in maternities, and later sent to the screening lab.

TREATMENT

The treatment for PKU should be initiated as soon as possible, preferably within the first week of life. The goal of treatment is to keep the Phe blood levels in the normal range for newborns. The measured Phe blood concentration in the first instance will direct the therapy, especially if the values are equal or greater than 360µmol / l2. The treatment for PKU has several guidelines, such as nutritional, pharmacologic and adjuvant.

NUTRITIONAL TREATMENT

The nutritional therapy relays in Phe food restriction. Is the mainstay in the treatment of deficiency in PAH, and it seeks to prevent the clinical consequences of this disorder, but providing an adequate nutritional support for the development of the individual [15].

Table 1. Dietary recommendations of Phe, Tyr and protein for patients with PKU2.

Age	Phe (mg/day)	TYR (mg/day)	Protein (g/kg)
0 to 3 months	130-430	1100-1300	3-3.5
3 to 6 months	135-400	1400-2100	3-3.5
6 to 9 months	145-370	2500-3000	2.5-3
9 to 12 months	135-330	2500-3000	2.5-3
1 to 4 years	200-320	2800-3500	≥30

Table 2. Energy Recommendations for individuals with PKU (Adapted: Macleod & Ney, 2010).

Age	Energy	
	Kcal/kg/dia	Kcal/day
0 to 6 months	95-145	----
7 to 12 months	80-135	----
1 to 3 years	----	900-1800
4 to 6 years	----	1300-2300
7 to 10 years	----	1650-3300

Men	Kcal/day	
11 to 14 years	2000-3700	
15 to 18 years	2100-3900	
≥ 19 years	2000-3300	
Women	Kcal/day	
11 to 14 years	1500-3000	
15 to 18 years	1200- 3000	
≥ 19 years	1400- 2500	

The overall goals of nutrition therapy are: to allow growth and cognitive development; maintenance of the individual's health status and allow gestational process without complications [8].

The diet therapy is directed towards limiting the Phe intake quantities that allow normal growth and development [16]. This therapeutic reiterates decreased of food intake in natural protein with partial replacement by artificial protein (aa's mixture) without Phe. Since the Phe is not naturally synthesized by the body and the excessive removal of this aa in the diet can lead to consequences, namely bone disorders, anorexia, anemia, diarrhea, severe eczema, malnutrition, and mental deficiency and seizures, the diet must be individualized and the treatment of PKU is no exception [17].

The amount of Phe present in each diet should vary according to the age, height, weight, growth rate and extent of the individual enzymatic deficiency and requires frequent adjustments, especially early in life.

The total nutrient intake should be known and monitored to ensure that the individual is not below a nutritionally adequate diet [5]. The diet for the treatment of PKU should reduce and control all kinds of foods rich in proteins, because all these foods contain Phe. This diet also eliminates sources "special" Phe, sweeteners such as aspartame containing aspartic acid and Phe. As a general rule, individuals with PKU for proper control of the disease must follow a vegetarian diet primarily or similar type (except grains such as beans), limited to fruits and vegetables, carbohydrate based foods or dietary foods especially designed for this type of pathologies, low protein food [5].

Development and evaluation of Phe's low dietary prescription

Nutritional therapy in PKU should be carried out, monitored and developed by a multidisciplinary team, with health professionals in the field of medicine, psychology, dietetics and geneticists.

Dietary prescription has to be individualized, built taking into account the nutritional requirements of protein and energy, according to the guidelines set out in Tables 1 and 2.

Phe and TYR

The Phe is an essential aa for protein synthesis and should be supplied in sufficient quantities to permit tissue repair, growth during childhood and protein turnover. Therefore, it is very important to maintain blood levels of Phe in accordance with Table 1. The Phe recommendations are identical for healthy individuals and for those suffering from PKU. The isolated Phe needs are difficult to interpret because this aa is also dependent of the TYR. So it is important to measure values are not only for Phe but also for TYR, and Phe / TYR ratio. TYR is an essential aa for PKU, given that the incapacity of Phe hydroxylation.

The supplementation in TYR is an adjunct nutritional therapy, but alone does not correct the phenotype of PKU. Therefore, aa mixtures also have in their constitution TYR. TYR is an insoluble aa, so if the individuals do not agitate the aa formula before consuming, they will not be able to eat it in sufficient amounts.

The Phe minimum recommended and the tolerated in the diet should be quantified individually, taking into account

the gene mutations for PAH and the ability for the synthesis and replacement of BH4 [14].

Phe dietary prescription for individuals with overweight or obesity should be estimated according to the reference weight for their height and age, because the needs in Phe are proportional to protein synthesis, which is reflected in the percentage of lean mass / muscle [22].

FOOD SCHEME

Breastfeeding

The PKU children can and should be breastfed by their mother, because breast milk contains the least amount of Phe that other sources of milk, powdered milk [14].

In infants with PKU their food should be done together with breast milk and a therapeutic milk product adapted for PKU patients [17].

Children suffering from PKU must be subject to a special food scheme, as follows:

- 1º Remove the child from the breastmilk for two or three days, and fed her with a bottle of milk replacers without Phe, adding maltodextrin, oil or olive oil and / or an hypoproteic milk formula, rich in carbohydrates, lipids, vitamins and minerals.
- 2º. After this period, evaluate the concentration of Phe in the blood and begin the breastfeeding again. The next food scheme should be five bottles / day of the milk replacer with maltodextrins, oil or olive oil or hypoproteic milk formula, and each bottle of milk should be followed by breast milk.
- Following this food scheme the child can be put to mother's breast whenever she wants [18].

Artificial breastfeeding

When the child is fed with milk powder for infants the food scheme should be the following:

- 1º. The milk powder is replaced by a milk replacer without Phe (PKU1 / or Lofenalac or Phenyl-Free) to which is added maltodextrins, or olive oil for three days. Then evaluate the value the blood levels.of Phe.
- 2º. Establish the formula of the bottle with the respective proportions of the milk substitutes, milk powder for infants, maltodextrins, or olive oil according Phe values in the blood.

Food diversification

Children with 4-6 months start another type of food, different for milk.

The diversification of food should start in children with 4-5 months if their are being fed with artificial breastfeeding, and in child fed by breastmilk should star at their 6th month.

In diversified diet begins with a gradual insertion of new foods in children's meals.

First begins with a starch pope or with a hypoproteic pope. Subsequently, should be introduced the soup, only with monitored weight vegetables and the fruit puree.

At 7-8 months the child can begin to eat cooked vegetables or stewed with cassava flour, corn porridge or mashed potatoes. By 8 months of age, can join orange juice to the pope, and so the infant could get ousted to the texture of the food, the soup should be less mashed, and introduce you to a grated carrot teaspoon or cooked carrots or cooked rice or boiled broccoli tips or mass.

At one year of age, the child can now dine with the family, with the necessary restrictions, and start trying to feed themselves alone. Instead of soup, the child must already consume whole vegetables boiled or stewed.

As mentioned earlier, all protein-rich foods are prohibited,

from either animal or vegetable origin [18].

Concept of "Part"

With the introduction of new food is also necessary to introduce the concept of "Part" to whom will prepare meals the child's meal.

"A Part of Phe corresponds to the weight of food in the grass that provides 20mg of Phe".

The creation of an equivalent table or "Parts" will help to make the concept of "part" easy to use.

The "Part System" (equivalent table) is used primarily with the establishment of the first soup. Thus, within the number of "Parts" advised and established by Nutritionist / Dietitian, for soup should use the food present in the equivalent table list respecting the corresponding weights to each of them. Proceeding to the same method for fruit and other allowed food.

It is desirable that foods containing Phe, as the protein substitutes, are ingested several times a day in order to minimize Phe fluctuations in plasma and ensuring optimal use of the remaining aa key.

The Portuguese Medical Genetics Institute (IGM) and other brands such as Loprofin, Milupa, Apofen, among others, offers the purchase of a range of products (flour, pasta, bread, etc.) with low Phe content and that children can use quite freely.

The IGM also create cookbooks, "Eat well ... no harm" Volume 1 and 2, as an auxiliary material for mothers in the use of dietary products3.

Duration and monitoring of dietary treatment

The duration of dietary treatment must be continued for life in order to maintain Phe blood levels within appropriate limits [15].

Previously, people with PKU interrupted the diet therapy even when they were children, leading to increased Phe blood levels. These patients began to show concentration and memory problems [19]. When these same individuals returned to the nutritional therapy, then they felt better and with less difficulty. So it's never too late to return to the diet, but the best option is never to leave her.

Nutritional treatment compliance

The purpose of the nutritional therapy is not only the patient fulfilment it, but also maintain it throughout the life cycle, because when abandoned is very difficult to re-enter.

Dietary compliance in PKU and their metabolic control is easily achieved in early childhood, in turn, at school age becomes increasingly difficult as the children begin to make their own food choices and develop their preferences and tastes. The dietary changes at this age, are associated with decreased aa mixtures consumption without Phe, although the enormous effort by the food industry to improve the organoleptic characteristics and design of packaging for these products.

Most children and adolescents refuses to consume aa formulas at school, leading to 8 hours/day without them. In the absence of consumption protein sources for 8 hours, the feeling of hunger settles, which also leads to deviant behavior, consume of products rich in Phe.

In adulthood, the diet that was abandoned during adolescence tends to be reintroduced in this age group. However, as previously mentioned, after the abandonment of dietary therapy is very difficult the recovery of restrictive eating behaviours. The absence of symptoms leads to motivational issues to maintain the food restriction.

It's important to create and design strategies to improve compliance or adherence to the nutritional therapeutic process. Such as:

- Health education sessions;
- Promote the creation of help groups where PKU patients can communicated with other PKU patients;
- Raise the investigation, evolution and adjustment of dietary prescription in accordance with the habits, tastes and preferences of the individual;
- Promote family involvement;
- Increase accessibility to health care and multidisciplinary team to the PKU patients [23].

NUTRITIONAL ADJUVANT TREATMENTS

Glycomacropeptide (GMP)

GMP is an intact whey protein, low in Phe, Tyr, histidine, leucine, tryptophan, and arginine, this protein represents a new option in detriment of the aa formulas. This protein has 64 aa's, whose chemical structure is specific due to the absence aa aromatic (Phe, Tryptophan, TYR) and high concentrations of isoleucine and threonine [3]. Several studies suggest that the use of GMP as a protein source allows a better use of the same, with decrease in concentration of ghrelin, which allows a greater satiety upon consumption of GMP products [8]. However, being a product without aa aromatics can take any need for supplementation thereof [24].

Large Neutral AA (LNAA's)

LNAA's have been proposed as a therapeutic adjuvant in PKU, based on its ability to block the use of the Phe in the intestine and the blood-brain barrier [2]. The use of LNAA's is not recommended for children or pregnant women, but may be considered for adults with PKU that do not have good metabolic control and who fail to adhere to other treatment options. When using this adjuvant therapy, 25-30% of protein needs are deleted with the LNAA's, the remaining 70-75% being acquired through dietary protein sources [8].

The protein intake and aa plasma should be monitored to prevent any deficiency framework of essential aa. However, the monitoring is difficult to treat with LNAA's, since Phe blood levels remained high and the quantitative evaluation of Phe in the brain is impractical. The melatonin in the blood and urine acts as biomarker for serotonin and can be useful in monitoring the treatment LNAA's, as PAH-deficient individuals have deficient amounts of serotonin [8].

PHARMACOTHERAPY

Sapropterin

The sapropterin (sapropterin dihydrochloride) is a pharmaceutical form of BH4, the cofactor required for the activity of PAH. This compound given in therapeutic doses seems to stimulate the activity of this PAH enzyme.

The advantages of this drug therapy fall into two types of patients, including: individuals who do not adhere or are unable to maintain dietary restrictions in protein and / or do not consume products with aa mixtures, wherein the sapropterin can decrease the concentration of Phe blood values without major dietary changes; and individuals who can control blood levels of Phe through diet therapy and wherein the sapropterin permits nutritional liberalization, either by reducing the consumption of aa mixtures, for enabling increased consumption of natural protein [8].

In Portugal, through the legislation order I n January of 2014, sapropterin, trade name KUVAN®, is provide without costs for patients with HFA / PKU. This treatment must be prescribed by Reference Hospitals for Hereditary Diseases Metabolism.

CONCLUSION

This state of art shows the importance of PKU treatment and early diagnosis as key factors for patients with this disease, in order to obtain quality of life, similar to healthy individuals.

Mental retardation stands out of all PKU manifestations, giving a prominent place to the early diagnosis of the disease, which must be made in the first days of life, in order to avoid possible damage.

PKU is a genetic disease due to an enzyme deficiency which has as a dietary, pharmacologic and adjuvant treatments. The nutritional therapy is characterized by reduction of any foods rich in protein. This patients use hypoproteic foods, together with some controlled essential proteins for a normal life cycle. The nutritional therapy is very rigid and should be maintained throughout lifetime. So is very importance to provide to this individuals and their families food education. The manifestations of PKU may be preventable through awareness of the importance of both early diagnosis and dietary treatment. Throughout this state of the art was possible to identify the major nutritional challenges, in particular:

- Keeping the Phe levels within the limits required for each individual;
- Achieving the energy and nutritional needs of these patients1;
- Lifelong nutrition education [20, 25];
- Preventing overweight / obesity [2];
- Prevent delays in growth [21].
- Monitoring Phe / TYR blood levels to constant adequacy of the diet [22].
- The food composition tables in Portugal do not include the necessary protein values, lack of quantification per year [6].

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