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Nutritional evaluation of children with phenylketonuria

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ABSTRACT

Context: Dietary phenylalanine (PA) restriction is the most effective form for reducing its excess in the blood and is the only efficient method for treating phenylketonuria. The diet is complex and should be adapted to combine the patients' eating habits, growth and development. It depends basically on the use of industrialized products as substitutes free of PA for proteins that are not fully supplied.
Objective: To evaluate the nutritional status of children with phenylketonuria (PKU) by anthropometric measurements and food intake.
Design: Cross-sectional study.
Setting: Children with PKU attending the Association of Parents and Friends of Handicapped Children (Associação de Pais e Amigos dos Excepcionais - APAE) and normal children attending at municipal day care centers in São Paulo.
Participants: 42 children with PKU and 31 normal children aged 1 to 12 of both sexes were assessed in two groups, under and over 7 years of age.
Main Measurements: Weight and height measurements.
Results: Children with PKU ingested calories, calcium, iron, zinc, and copper below the recommended values, whereas the protein intake was within the normal range. Food intake in the group of normal children was within normality rates. The height/weight Z-score means for children with PKU were 0.47 for those under 7 years and 1.86 for 7 year-olds and over; in normal children the means were 0.97 <7 years and 1.54 ≥7 years, with no statistically significant difference. The height/age Z-score means were significantly lower in the PKU children <7 years (-1.23) than in the normal controls (0.91).
Conclusions: The data presented demonstrate the importance of nutritional surveillance in patients with PKU so as to support adequacy of nutrient intake and to guarantee growth within the relevant standards.
Key words: Phenylketonuria. Artificial diets. Anthropometric measurements.

INTRODUCTION

Dietary phenylalanine (PA) restriction is the most effective form for reducing its excess in the blood and is the only efficient method for treating phenylketonuria.[1] The diet is complex and should be adapted to combine the patients' eating habits, growth and development.[2] It depends basically on the use of industrialized products as substitutes free of PA for proteins that are not fully supplied.

Whitehead[3] observed that the main interest in the follow-up of patients with this disease is focused on the proteins, but that it is essential to consider protein requirements within the context of energy. He stated that energy consumption should be monitored by anthropometric measurements such as weight and height. In a collaborative study on 113 children in phenylketonuria (PKU) treatment centers in the US, growth standards were normal.[4]

In Brazil, Fisberg et al[5] evaluated 60 children with PKU using continuous anthropometric assessment methods, showing that as the time of treatment became more delayed, there was a worsening of weight and height data in the late-diagnosed group (diagnosed after 3 months of age). Thus, restricted diets may lead to various

disorders of the economy of human beings, reflected in growth and development alterations that depend on the time of appearance of the disorder, duration of nutritional privation and degree of severity of the disorder. Therefore, based on these facts, we resolved to evaluate the nutritional status of PKU children.

METHODS

Participants

Forty-two PKU children aged 1 to 12 years of both sexes took part in this study, divided into two groups: under 7 years old (n = 24), and 7 and over (n = 18). They were followed up at the Association of Parents and Friends of Handicapped Children (Associação de Pais e Amigos dos Excepcionais - APAE). The control group comprised 31 normal children (< 7 years n = 9; ≥ 7 years n = 22), who attended municipal day care centers in São Paulo and presented characteristics similar to those of the PKU group.

The children were divided into two age groups because the average amount of the special product to be offered to the children differed between the two age groups, following the product usage instructions given by the manufacturer.

The procedures followed were in close agreement with the ethical standards of the Ethics Committee of the Federal University of São Paulo, and were thus approved by its members.

Dietary assessment

Dietary assessments of children with PKU were recorded on a special form developed for a 3-day study, 2 days being in the middle of the week and 1 day during the weekend.[6] The dietary formula used for children with phenylketonuria was PKU2 (Milupa, Friedrichsdorf, Germany). In the group of normal children, food intake was evaluated by the weighed food record.[7] Standardization of measurements of meal portions was achieved by choosing the most suitable utensil for each kind of food. The amount served was established according to what children were used to ingesting. In addition, the same amount of food was served to all the children. Afterwards, food served randomly to three children at each meal was weighed to know the average amount offered. The average amount of food ingested at each meal was obtained by adding the total amount of food offered to the total amount of repetitions, and then subtracting from this value the amount of leftovers. In order to obtain this data, the leftovers were collected in plastic bags, identified with each child's name, and weighed without separating the food, using domestic scales with a capacity of 5 kg and graduations of 10 mg. For fluid food a plastic glass with graduations of 50 ml and capacity of 500 ml was used. The method was used for 2 days for each child and the mean, obtained as described above, was used as the reference for adequacy of intake among the group of normal children, in relation to their recommended diet.

Calculation of the intake of calories, protein, lipid, carbohydrate, calcium, iron, zinc and copper was done using computer software.[8] When any food that was not listed in the software data base was ingested, the Table of Food Composition from the National Study of Family Expenses was used, together with Souci et al.[9,10] For diet adequacy purposes, the Recommended Dietary Allowances (RDA)[11] were used as standard.

We used the following calculation to obtain the percentage adequacy of the ingested in relation to the recommended: % adequacy = [(ingested x 100)/recommended].

The methodology for the evaluation of food intake of an individual or a group depends on the objectives of the project and on their feasibility and application. In order to use two different methods of evaluating food intake, the groups were not compared to each other. The food evaluation in the control group had the aim of demonstrating that these children were not restricted either regarding quantity or quality of food.

Anthropometric measurements

Weight and height measurements were taken of normal and PKU children. All children

were weighed using an anthropometric scale while only wearing underwear, and after prior qualification by the examiner. For children below 2 years, height was measured with an anthropometric ruler, and the patient was in dorsal decubitus. For children over 2 years old, a mobile stadiometer was used for measuring standing height. The children stood with their backs to the stadiometer, heels aligned and flat on the floor, knees in a straight position, body and head leaning on the stadiometer; a wooden, wide-based square with an angle of 90° was lowered over the child's head. Standardization and quality control of anthropometric measurements were carried out according to the recommendations of Lohman et al.[12] The calculations of the anthropometric ratios of weight for age (W/A), height for age (H/A) and weight for height (W/H) were carried out using computer software,[13] with distributions analyzed as Z-scores based on NCHS reference data.[14]

Statistical Methods. To analyze the results, we applied the Mann-Whitney Test[15] so as to compare the age groups of children in relation to the studied variables. This was done by evaluating the fit to the normal distribution curve (statistic Z) when the sample size required this.

RESULTS

According to the data shown in Table 1 and Figure 1, referring to the two groups studied, the protein intake was adequate when compared to the standard recommended diet.[11] Nevertheless, when we analyzed the average protein intake of the group of normal children, this represented twice (273%) the suggested protein amount and this finding was similar to other studies. The recommended intake of phenylalanine was obtained in 90 to 100% of the menus and this is reflected by the protein adequacy presented by the studied group. Children with PKU ingested average percentages of calories and nutrients with the exception of copper in ≥ 7 year olds, which was lower than the recommended (Table 1).

There was a substantial difference between the diet adequacy averages found for calcium, iron and copper intake in children with phenylketonuria. The eating pattern followed by PKU children excluded foods that were sources of animal protein. The following foods were included in their diet: cereals, breads, tubers, roots, fruits and vegetables, in controlled amounts depending on the characteristics of the child. The patients were given examples of menus with a list of equivalents for substitution, and it should be noted that the menus were devised taking into account the children's preferences, ease of preparation and amount of phenylalanine, to the detriment of other nutrients required for growth. In the control group the mean percentage of ingestion adequacy reached at least two-thirds of the recommended diet during their stay in the day-care institution, showing that this group was not at risk of impairment of its nutritional status. The children stayed in the institution until late afternoon, receiving two snacks, lunch and soup in the afternoon, with dinner at home expected to complement the day's nourishment.

The weight for height (W/H) and weight for age (W/A) values in children with phenylketonuria did not show any substantial differences when compared to normal children (Tables 2 and 3). The mean Z-score of height for age (H/A) showed statistically significant differences between normal children and the patients with phenylketonuria < 7 years (Table

Table 1 - Mean daily intake percentages of calories, proteins, calcium, iron, zinc and copper of children with phenylketonuria, according to age

Age	Calorie	Protein	Calcium	Iron	Zinc	Copper
< 7 years	62.6 (19)	105.0 (32)	56.1 (12)*	72.3 (20)*	36.6 (14)	85.8 (26)*
≥ 7 years	60.5 (14)	109.4 (19)	65.5 (25)*	94.0 (20)*	38.5 (9)	104.1 (31)*

* p ≤0.05 (<7 years is less than ≥7 years); Standard deviation given in parenthesis.

4), but within normality rates. In the evaluated groups of PKU children < 7 years and ≥ 7years, the low height percentages were 50% and 22%, respectively. These percentages were higher than those found in normal children (< 7 years - no children and ≥ 7 years - 18%).

DISCUSSION

The calorie intake results showed that it was more difficult for children with PKU to obtain recommended calories than protein, since the special formula supplied a small amount of calories. Another factor that needed to be taken into account was that the amount of ingested phenylalanine had to be controlled. Different foods were included in the diet according to preference, children's acceptance, and ease of preparation and acquisition, and were not always substituted for adequate calorie equivalents. We normally used fats and sugars to increase the total calorie intake. Nevertheless, children did not always accept the greater amounts of oil in food preparation as age increased. We did not have at our disposal low-protein foods to increase the calorie intake.

The results highlight the fact that it is not always possible to follow recommendations for children with PKU who need low protein foods. Adequate calorie intake prevents the use of protein as a source of energy. The average calcium intake by children with PKU < 7 years was substantially lower than by children ≥ 7 years, because as age increased, a greater amount of PA-free medical food was taken. Consequently, the amount of calcium ingested increased as a percentage of RDA.

Another factor that should be taken into account is that with increasing age, PA intake increases and other food calcium sources can be used in greater amounts such as milk and cream in the formulae, thus increasing the content

Table 2 - Distribution of weight for height (W/H) Z-score of children with phenylketonuria (PKU) and normal (N), according to age

	Normal < 7years	PKU < 7years	Normal ≥ 7 years	PKU ≥ 7 years
ZW/H	0.97 (1.18)	0.47 (1.06)	1.54 (3.50)	1.86 (3.13)
% -2 ZW/H	-	-	-	-
% +2 ZW/H	22.2	12.5	13.6	22.2

Standard deviation given in parenthesis

Table 3 - Distribution of weight for age (W/A) Z-score of children with phenylketonuria (PKU) and normal (N), according to age

	Normal < 7years	PKU < 7years	Normal ≥ 7years	PKU ≥ 7years
ZW/A	1.17 (1.47)	-0.44 (1.08)	0.11 (1.20)	0.30 (1.12)
% -2 ZW/A	-	4.2	-	-
% +2 ZW/A	22.2	-	9.1	5.6

Standard deviation given in parenthesis

Table 4 - Distribution of height for age (H/A) Z-score of children with phenylketonuria (PKU) and normal (N), according to age

	Normal < 7years	PKU < 7years	Normal ≥ 7years	PKU ≥ 7years
ZH/A	0.91 (1.26)*	-1.23 (0.84)*	-0.05 (1.03)	-0.32 (0.91)
% -2 ZH/A	-	16.7	4.5	5.6
% +2 ZH/A	22.2	-	-	-

*p ≤ 0.05 (PKU < 7 years is less than normal < 7 years); Standard deviation given in parenthesis

of this nutrient. The mean calcium intakes of children with PKU, as a percentage of RDA, found by Acosta et al[16] were 84 to 136%. The formula used in that study was Phenyl-Free, which has a greater amount of calcium per gram of protein than that found in PKU2. The 10 subjects assessed in that study were between 3 and 13 years old and other food sources that would lead to a better intake of this nutrient were not mentioned.

In the present study, the adequacy of iron intake by the children with PKU was better than for calcium. Gropper et al[17] found that the iron intake by children with PKU (4 to 7 years old, 199% and 7 to 11 years old, 296%) was higher than that of the control group (126% and 174% respectively), being greater than RDA in both groups. Data provided by Acosta et al[16] showed that iron intake by children with PKU was above the RDA. Nevertheless, some children had indices of iron nutrition status below normal values. Scaglioni et al[18] found concentrations of serum ferritin substantially lower in the children with PKU than in normal children. However, other evaluated indices of iron nutrition status did not differ among the groups.

Longhi et al[19] studied children with PKU and found iron intake to be 65% of the recommended. In the age group from 12 to 26 months, these rates were exactly the same as those found in our study (62%). When the age group from 5 years and 9 months to 10 years and 10 months (9 children) was evaluated, the adequacy of iron intake was 164% of RDA. However, the high intake of non-heme iron and its low availability could interfere with the absorption of this element. Despite the fact that iron intake in our study reached lower values than those referred to in the previous literature, our group with PKU had a low prevalence of anemia (18%), when compared with São Paulo State data.[20] In our diet, children used modified powdered milk in amounts that supplied up to 15% of RDA for iron. In children under 7 years, this percentage is above what PKU2 would supply (13%).

Longhi et al[19] also showed that the mean amount of zinc ingested by children with PKU was 64% of RDA. The same low values were found by Acosta et al.[21] These patients had an intake below 100% of RDA and 38.5% were below 67% of RDA.

We highlight the fact that, for other evaluated nutrients (calcium, iron, copper), a greater amount of PKU2 was used as the group age increased, which consequently increased the percentage of the attained RDA. This did not happen in the case of zinc. It may not only have been the increase in the special formula that led to increased adequacy, but also the inclusion of other foods in greater amounts. Foods which are sources of zinc, both of animal origin (meats, fish and seafood) and vegetal origin (whole grains, chestnut and leguminous plants) were completely absent from the diet.

The food sources of zinc and copper are similar, but their distributions were found to be different when we evaluated the diet. As the diet was composed basically of vegetables (with the exclusion of leguminous ones) and fruits, meeting a recommendation for 1 mg copper was easier than meeting one for 10 mg zinc. In balanced diets, containing adequate amounts of all foods, this does not occur, since 100 g beef corresponds to 87.5% of RDA for zinc.

With total restriction of sources rich in animal proteins and trace elements, children with PKU cannot maintain an adequate intake of zinc and other metals if the medical food is

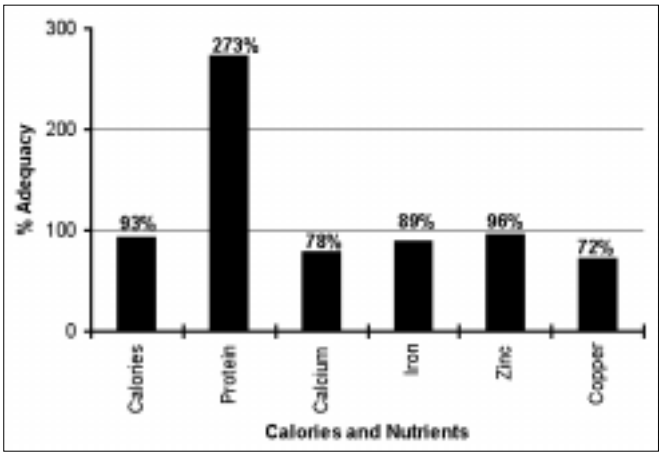

Figure 1 - Mean daily intake percentages of calories, proteins, calcium, iron, zinc and copper of normal children.

inadequately supplemented.

Values equal to or higher than those suggested for the intake of copper were also found by other authors.[16.17.19] We conclude that the special formulae meet the needs for most trace elements, but this does not happen with zinc and iron.

Children with PKU are normal when they are born, since phenylalanine hydroxylase in the mother's liver will metabolize phenylalanine. The weight at birth is not changed because of the illness.[5] Accordingly, growth depends on the amount of PA ingested and adequacy of blood PA concentrations as well as the adequacy of intake of protein and energy.

Sibinga et al,[22] while studying 60 children with PKU receiving treatment, found a substantial growth decrease (weight and height), regardless of the age at which the diet was initiated. When these results were compared to those from other centers, they concluded that phenylketonuria, or its treatment, were associated with height decrease. Our results show a greater relationship between protein intake and height of such patients. It is probable that for growth, not only is protein adequacy necessary, but also dietary balance as a whole.

We have already described that the diet ingested by children with PKU in our study met all protein needs. However, the recommended energy intakes were not reached, and part of the protein was probably used by the body as a calorie source. Phenylketonuria diets are able to maintain weight for height indices. Either the child with PKU suffers an adaptation to the ingested nutrients or, as the group age increases, the restrictions are reduced and greater amounts of foods are ingested (special formula and natural sources) leading to nutritional recovery.

We must point out that during the treatment we used PKU1, which meets the nutritional needs of infants with PKU up to the completion of their first year of life, and PKU2 after this age. PKU2 has half the amount of iron and one third of the amounts of zinc and copper of PKU1. On the other hand, as the group age increases, other natural foods are added. Thus, the intake of trace elements does not meet the recommended level,[19] leading to lower growth.

CONCLUSION

These data suggest that further studies should be carried out with longitudinal observation of PKU children. The amounts of trace elements, especially zinc, in special formulae should be revised in order to adapt the diet better to RDA and to the evaluation of growth channels.

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RESUMO

Contexto: A restrição dietética da fenilalanina (FAL) é a forma mais efetiva para reduzir o seu excesso no sangue e o único método efetivo de tratar a fenilcetonúria. A dieta é complexa e deve ser adaptada para combinar hábitos alimentares, crescimento e desenvolvimento dos pacientes. Depende basicamente do uso de produtos industrializados como substitutos protéicos isentos de FAL, não totalmente suplementados. **Objetivo:** Avaliar o estado nutricional das crianças fenilcetonúricas por medidas antropométricas e o consumo alimentar. **Tipo de estudo:** Estudo transversal **Local:** Associação de Pais e Amigos dos Excepcionais (APAE) de São Paulo, Creche e Centro de Juventude da Prefeitura de São Paulo. **Participantes:** 42 crianças fenilcetonúricas e 31 normais, na faixa etária de 1 a 12 anos, divididas em dois grupos abaixo e acima de 7 anos, de ambos os sexos. **Resultados:** As fenilcetonúricas apresentaram porcentagem de adequação da ingestão de calorias, cálcio, ferro, zinco e cobre abaixo do recomendado. A ingestão protéica estava dentro da normalidade. O consumo alimentar no grupo de crianças normais apresentou-se dentro da faixa da normalidade. As médias de peso para estatura em escore z das fenilcetonúricas foram 0.47 < 7 anos e 1.86 ≥ 7 anos; nas normais 0.97 < 7 anos e 1.54 ≥ 7 anos, sem diferença estatisticamente significante. As médias de E/I apresentaram diferença estatisticamente significante entre fenilcetonúricas < 7 anos (- 1.23) e crianças normais de mesma faixa etária (0,91). **Conclusão:** Concluiu-se que a vigilância nutricional em crianças fenilcetonúricas é importante para manutenção dos padrões de crescimento e o adequado consumo de nutrientes.
Palavras-chave: Fenilcetonúria. Dietas artificiais. Antropometria.