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Evaluation of Physical Growth and Weight Patterns of Egyptian Children with Phenylketonuria under a Phenylalanine-Restricted Diet

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Abstract

Objective: A phenylalanine-restricted diet is the mainstay of phenylketonuria (PKU) treatment but does not normally provide enough protein for growth requirements. We evaluated the effect of a phenylalanine-restricted diet on growth parameters of Egyptian children with PKU.

Methods: Twenty-eight PKU children were evaluated for weight, height, and body mass index (BMI) and were compared with matched controls at baseline and then their baseline parameters were compared with those collected 2 years later.

Results: At baseline, 86% of PKU children were normal weight and 11% below; and 75% were in the normal height percentile and 25% below. For BMI, 68% were normal, 21% overweight and 11% obese. Two years later, all PKU children were in the normal weight percentile, and 79% were in the normal height percentile and 21% below. For BMI, 46% were normal, 36% overweight and 18% obese. For PKU children below normal percentile at baseline, normal weight, but not height, was reached after 2 years. Also, more PKU children became overweight or obese after 2 years.

Conclusions: Early detection of PKU and early use of a phenylalanine-restricted diet may avoid growth retardation of height, but care should be taken to avoid patients becoming overweight or obese over time.

Keywords: Phenylketonuria; Phenylalanine-restricted diet; Physical growth; Weight

Abbreviations

BMI: Body Mass Index; NA: Not Applicable; PKU: Phenylketonuria; SD: Standard Deviation

What's New

Phenylalanine-restricted diet does not provide enough protein for growth requirements in children. After 2 years, most children with phenylketonuria who were below the 3rd percentile for both, weight and height, reached normal growth for weight but not for height.

Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism resulting from deficiency of phenylalanine hydroxylase [1]. A Phe-restricted diet is the mainstay of PKU treatment [2]. Protein intake is calculated each day, and the patient is allocated a certain number of units of daily protein, depending on longitudinal plasma Phe concentrations. Foods that are high in protein, such as eggs, milk, cheese, meat, poultry, fish, dried beans, and legumes, are excluded from the diet [3].

However, evidence suggests that a Phe-restricted diet does not provide enough protein for growth requirements in children and causes a risk of imbalances in essential dietary nutrients [4] In addition; these patients may have low concentrations of trace elements and cholesterol, some disturbance in folate metabolism, and distortion of their fatty acid profile [5-7].

Current evidence suggests that growth in early childhood for PKU children is suboptimal relative to non-PKU control groups or reference populations [8]. In one study, PKU children had almost identical height but greater weight compared with age-matched controls [9].

The incidence of PKU in Arabic populations is approximately 1 in 6000 births, which is relatively high compared with other regions and countries [10]. In spite of this high incidence, longitudinal studies investigating the effect of a Phe-restricted diet on physical growth in Arabic PKU children are lacking. Therefore, the aim of the current study was to evaluate the effect of a Phe-restricted diet on the physical growth of Egyptian children with PKU.

Methods

Egyptian children diagnosed with PKU, who were patients at the pediatric clinic of the National Research Centre in Giza, Egypt, were recruited for the current study. The potential participants had to be clinically diagnosed with PKU, and the diagnosis had to be confirmed

by measurement of blood pH level. Potential participants were excluded from the study if they had mental, social, or congenital anomalies. Informed consent for participation in the study was obtained from the parents of the children according to guidelines established by the ethical committee of the National Research Centre in Giza, Egypt, and according to the World Medical Association Declaration of Helsinki sixth revision guidelines [11].

Supervisors at the National Research Centre ensured that patients were provided with fresh vegetables and fruits in addition to low protein (starch) diet [12]. Diet compliance was determined by patient report. Blood Phe levels were also collected each month according to established guidelines [13].

At the start of the current study (baseline), anthropometric measurements including weight (using a digital balance), height (using a stadiometer), and body mass index (BMI) were obtained following standardized techniques [14]. The BMI was calculated according to BMI = weight/height^2 (kg/m^2). From these measurements, z-scores for weight and height were calculated according to World Health Organization Child Growth Standards [15]. The z-score was used as an index of severity of PKU. Growth chart data from the United States Department of Health and Human Services Centers for Disease Control and Prevention (CDC) were used to calculate weight, height, and BMI percentiles for comparisons [16]. We used the CDC data for the current study because it is comprehensive and because Egypt lacks a similar database.

For baseline measurements, the weight, height, and BMI of PKU children in the current study were also compared with age- and sex-matched controls. The control group data was a convenience sample of existing anthropometric measurements of healthy children who were also patients at the pediatric clinic of the National Research Centre in Giza, Egypt.

After 2 years, weight, height, BMI, z-score for weight, z-score for height, and growth chart data percentiles from the CDC16 for PKU children were compared with the baseline outcomes for the PKU children and with the matched controls. For weight and height percentile data, we used the following categories for comparisons: below the 3rd percentile, normal (between 3rd and 97th percentiles), and above the 97th percentile. For the BMI percentile data, children were classified into the following BMI categories as defined by the CDC16: underweight (BMI less than the 5th percentile), normal weight (BMI between the 5th and 84th percentile), overweight (BMI between the 85th and 94th percentile), or obese (BMI more than the 94th percentile).

The collected data were analyzed using statistical software SPSS version 20 (IBM, Armonk, NY). Results were expressed as mean and standard deviation (SD), percentage, or median and range as appropriate. An independent t test was used to compare the PKU children and the age- and sex-matched control children, and a paired t test was used to compare the changes in the PKU children from baseline to 2 years later. The quantitative data were examined using a Kolmogrov Smirnov test for normality. A P value less than .05 was considered statistically significant. For the weight and height z-scores, a score between -2 and +2 was considered within the normal range [17].

Results

Twenty-eight Egyptian children diagnosed with PKU participated in the current study: 17 were males (61%) and 11 were females (39%). The mean (SD) age of the PKU children at baseline was 7.2 (3.4) years, the median age was 6.5 years, and the age range was 3-14 years. All participants returned 2 years later to complete the study.

Baseline Measurements

Compared with the matched control group at baseline, the PKU children had lower mean (SD) weight (24.8 [11] vs 33 [15.6] kg, P=.02) and height (116.6 [20.7] vs 128.4 [18.7] cm, P=.01) (Table 1). There were also significant differences for the z-score for weight (P=.009) and height (P=.005) and for the weight percentile (P=.01) and height percentile (P=.03) data from the CDC. There was no difference in BMI (P=.08) or the BMI percentile (P=.7) data for the PKU children compared with the control group at baseline.

Growth Parameter	PKU Baseline, Mean (SD)	PKU 2 Years Later, Mean (SD)	Matched Controls, Mean (SD)	t Statistic, P Value[a]	
				Baseline vs Control	Baseline vs 2 Years Later
Weight, kg					
Weight	24.8 (11)	32.7 (13.9)	33 (15.6)	2.3, .02	2.3, .02
z-score	-0.2 (1.2)	0.1 (0.9)	0.6 (1.2)	2.6, .009	1, .2
Percentile	43 (28.2)	60.1 (26.6)	61.5 (29)	2.6, .01	2.3, .02
Height, cm					
Height	116.6 (20.7)	128.3 (20.3)	128.4 (18.7)	2.4, .01	2.1, .03
z-score	-0.9 (1.1)	-0.9 (1.3)	-0.16 (1.1)	2.8, .005	0.02, .9
Percentile	30.1 (29.7)	33.3 (29.1)	46.1 (31.3)	2.1, .03	0.3, .7
BMI					
BMI	17.3 (2.4)	26.2 (9.4)	18.9 (4.1)	1.7, .08	1.1, .2

Percentile[b]	62.5 (27.5)	74.8 (20.6)	60.7 (25.9)	0.2, .7	1.8, .06

[a]P values less than .05 were considered statistically significant.

[b]BMI percentile was obtained from growth chart data from the United States Department of Health and Human Services Centers for Disease Control and Prevention.

Abbreviations: BMI, body mass index; PKU, phenylketonuria; SD, standard deviation.

Table 1: Comparison of growth parameters of Egyptian children with phenylketonuria (N=28) at baseline and 2 years later compared with age- and sex-matched controls (N=42).

Measurements of PKU Children 2 Years Later

After 2 years, the mean (SD) weight (32.7 [13.9] kg, P=.02) and height (128.3 [20.3] cm, P=.03) of the PKU children increased (Table 1). Weight and height z-scores and weight and height percentile data also increased after 2 years, but only the weight percentile increased significantly (P=.02). The BMI (17.3 [2.4] vs 26.2 [9.4]) and BMI percentile data (62.5 [27.5] vs 74.8 [20.6]) increased after 2 years, but not significantly.

Comparisons of Percentile Data of Growth Parameters

For the weight percentile at baseline, 24 (86%) PKU children were in the normal percentile, 3 (11%) were below the 3rd percentile, and 1 (4%) was above the 97th percentile (Table 2). For height, 21 (75%) were in the normal percentile, and 7 (25%) were below the 3rd percentile. For BMI, 19 (68%) were normal, 6 (21%) were overweight, and 3 (11%) were obese.

After 2 years, the weight percentiles of all the PKU children were normal (Table 2). For height, 22 (79%) were in the normal percentile, and 6 (21%) were below the 3rd percentile. For BMI, 13 (46%) were normal, 10 (36%) were overweight, and 5 (18%) were obese.

For the weight of the matched control group children, 37 (88%) were normal, and 5 (12%) were above the 97th percentile (Table 2). For height, 37 (88%) were normal, 4 (10%) were below the 3rd percentile, and 1 (3%) was above the 97th percentile. For BMI, 30 (72%) were normal, 2 (5%) were underweight, and 10 (24%) were overweight.

(Growth Chart Data)[a] Percentile Range	**PKU Baseline**			**PKU 2 Years Later**			**Matched Controls**		
	No. (%)	**Mean (SD)**	**Median, Range**	**No. (%)**	**Mean (SD)**	**Median, Range**	**No. (%)**	**Mean (SD)**	**Median, Range**
Weight									
Below 3rd percentile	3 (11)	2 (0)	2, 0	0	NA	NA	0	NA	NA
Normal	24 (86)	45.8 (23.9)	50, 85	28 (100)	60.1 (26.6)	65, 85	37 (88)	56.7 (27.6)	50, 85
Above 97th percentile	1 (4)	98 (0)	98, 0	0	NA	NA	5 (12)	98 (0)	98, 0
Height									
Below 3rd percentile	7 (25)	2 (0)	2, 0	6 (21)	2 (0)	2, 0	4 (10)	2.5 (0.5)	2, 1
Normal	21 (75)	39.5 (28.7)	25, 85	22 (79)	41.5 (27.5)	25, 85	37 (88)	49.4 (28.7)	50, 85
Above 97th percentile[b]	0	NA	NA	0	NA	NA	1 (3)	98 (0)	98, 0
BMI[c]									
Underweight	0	NA	NA	0	NA	NA	2 (5)	17.3 (1.2)	17.3, 1.8
Normal	19 (68)	49.6 (24)	50, 76	13 (46)	56.7 (16.4)	60, 52	30 (72)	18.9 (4.4)	17.8, 17.8
Overweight	6 (21)	86.8 (3.2)	85, 8	10 (36)	87 (3.5)	86, 9	10 (24)	19.1 (3.9)	17, 10.4
Obese	3 (11)	95.8 (1.4)	95, 2.5	5 (18)	96 (0.7)	96, 2	0	NA	NA

[a]Growth chart data were obtained from the United States Department of Health and Human Services Centers for Disease Control and Prevention.

[b]Percentages may not add to 100% because of rounding.

[c]BMI percentile was defined using the following categories: underweight (BMI < 5th percentile), normal weight (BMI in the 5th to 84th percentile), overweight (BMI in the 85th to 94th percentile), or obese (BMI > 94th percentile).

Table 2: Comparison of growth chart data of Egyptian children with phenylketonuria (N=28) at baseline and 2 years later compared with age- and sex-matched controls (N=42).

Discussion

Although research in recent years has focused on non-dietary treatments of patients with PKU, diet is likely to remain the primary treatment for many years [18]. For children with PKU, careful monitoring of the Phe-restricted diet is especially important because poor nutrition can impair growth and may cause long-lasting health effects.

In the current study, the baseline weight of Egyptian children diagnosed with PKU was significantly less than the weight of the age- and sex-matched control group children even though only 3 PKU children were below the 3rd percentile for weight. The z-score for weight for the PKU children was within the normal range for growth [17] despite being significantly different from the control group. After 2 years, the weight of PKU children showed statistically significant improvement from baseline, and all PKU children were within the normal weight percentile as defined by CDC growth chart data [16]. Thus, the 3 PKU children who were below the 3rd percentile for weight at baseline reached normal growth after 2 years. This result is supported by a previously published study that found the normal growth curve for PKU children was restored after the second year, when the diet was less restricted [19].

Similar to the weight findings of the current study, the height of the Egyptian children with PKU was significantly less than the height of the matched control group children. The z-score for height was in the normal range for the PKU children, and 7 PKU children were below the 3rd percentile for height; both of these results were significantly different from the control group. In a previous study, PKU patients were found to be shorter and lighter than the reference population [20]. After 2 years, the PKU children of the current study were significantly taller than at baseline. However, the z-score for height and the height percentile comparisons were no longer significantly different. This result may be related to the 7 PKU children below the 3rd percentile for height at baseline; after 2 years, only 1 child reached normal growth. The improvement of height after proper control of diet is of great importance in clinical practice to avoid the growth retardation of height, which is difficult to correct after closure of the epiphyseal cartilage.

For comparisons of BMI and BMI percentiles, there were no significant changes between the PKU children and the matched control group children. Further, none of the PKU children, either at baseline or 2 years later, were underweight according to the BMI categories defined by the CDC [16]. Two of the age- and sex-matched control group children were underweight, however.

Of the 28 Egyptian children diagnosed with PKU who participated in the current study, 24 were in the normal weight percentile at baseline, and all were in the normal weight percentile 2 years later. Twenty-one were in the normal height percentile at baseline, and 22 were in that percentile 2 years later. Nineteen children were in the normal percentile for BMI at baseline, and 13 were in the normal percentile for BMI 2 years later. These percentile results suggest that most of the PKU children of the current study reached normal growth for weight and height after 2 years. These normal growth results were only found for weight and height.

For BMI, fewer children were in the normal percentile after 2 years. At baseline, 6 PKU children were overweight and 3 were obese. After 2 years, 10 were overweight and 5 obese. The recommended diet of children with PKU does not limit carbohydrate or fat intake [17]. Therefore, the nutritional caloric intake of the PKU children of the current study may have exceeded their energetic needs. Other possible risk factors of being overweight are lower socioeconomic status (for both sexes) and overweight parents and large stature (for girls only) [21].

After an initial period of growth retardation, the Egyptian children diagnosed with PKU in the current study had a significant increase in weight and height. Further, those children below the 3rd percentile for weight at baseline reached normal growth after 2 years, but most of those below the 3rd percentile for height did not reach normal growth after 2 years. Previously published European studies found growth retardation of PKU patients during the first years of life was followed by restoration of normal growth [9, 22-24] A longitudinal study of Dutch children found that those with PKU had an almost identical height as other children of the same age [9]. Although normal growth appeared to be restored for weight in the current study, the normal growth for height for the PKU children was not restored. In Egypt, there is a lack of national screening programs for early detection of PKU, especially in neonates. Thus, a late onset of diagnosis for PKU patients and a delayed initiation of a Phe-restricted diet may explain the observed differences of weight and height between the current study and previous studies.

In conclusion, most of the Egyptian children diagnosed with PKU in the current study were within the normal growth percentiles for weight and height. However, a small percentage of the children were below the 3rd percentile for weight and height. After 2 years, most of these reached normal growth for weight but remained below the 3rd percentile for height. In addition, many of the PKU children gained weight after 2 years and became overweight or obese. Based on the results of the current study, we recommended the early detection of PKU and the early use of a Phe-restricted diet to avoid the growth retardation of height, which is difficult to correct. Also, care should be taken during the treatment of PKU patients to avoid patients becoming overweight or obese over time.

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