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Breastfeeding in the treatment of children with phenylketonuria

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Abstract

Objective: To evaluate the effect of breastmilk as a source of phenylalanine (phe) on levels of this amino acid and on growth in phenylketonuric infants.

Methods: The study recruited 35 breastfed phenylketonuric infants and compared their results with those of 35 infants fed on commercial, milk-based formula. The groups were paired for sex and age at weaning from breastfeeding. Data were analyzed up until cessation of breastmilk or for 12 months' follow-up. The breastfed group were given a "special formula" free of phe, by bottle every 3 hours, and breastmilk at will during the intervals. Levels of phe in the blood, collected weekly up to 6 months and fortnightly up to 1 year of age, were analyzed while breastfeeding continued. The two groups were compared in terms of the time taken for the levels of phe in blood to return to normal after treatment was started, using the Wilcoxon test. Anthropometric data were compared with Student's t paired test in the form of z scores. The phe assays were analyzed throughout breastfeeding.

Results: The median time taken for phe levels to return to normal was 8 days for the breastfed group and 7 days for the control group. The phe assay results were normal in 87% of tests for the breastfed group and in 74.4% for the control group. The majority of children in both groups exhibited a z score > -2 on anthropometric examination.

Conclusions: Continuation of breastfeeding, during the treatment, proved adequate for metabolic control and growth in children with phenylketonuria.

J Pediatr (Rio J). 2007;83(5):447-452: Breastfeeding, phenylketonuria, phenylalanine.

Introduction

Phenylketonuria (PKU) is an autosomal recessive genetic disease, characterized by either a deficiency or even absence of phenylalanine hydroxylase enzyme activity, which prevents hydroxylation of phenylalanine (phe) into tyrosine. The

increased levels of phe in the blood then lead to central nervous system abnormalities, causing irreversible mental retardation.¹

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Gerais), which is managed by the Center for Actions and Research in Diagnostic Support (NUPAD - Núcleo de Ações e Pesquisa em Apoio Diagnóstico) at the Medical Faculty of the Universidade Federal de Minas Gerais (FM-UFMG), is responsible for neonatal screening in the state of Minas Gerais, Brazil. All children with phe levels ≥ 4 mg/dL are referred to the Special Genetics Service at the Hospital das Clínicas, UFMG (SEG-HC-UFMG), for diagnostic elucidation and treatment, if needed.² According to the Brazilian Health Ministry's protocol (Directive SAS/MS 847/2002), all children with levels of phe in blood ≥ 10 mg/dL must be treated. Treatment is based on a diet that restricts phe, associated with a protein substitute to make up daily protein requirements, in particular.²⁻⁴ The blood phe levels considered adequate for phenylketonuric patients during their first year of life should be ≥ 2 mg/dL ≤ 6 mg/dL.⁵ Since phe is also an essential amino acid for phenylketonuric patients, their diet must contain the correct amount, making it possible to maintain blood levels within limits considered safe while also maintaining the patients' growth and development within the parameters of normality.³ The traditional treatment for PKU includes the recommendation to withdraw breastmilk (BM) due to the difficulties involved in quantifying children's phe intake and, consequently, in controlling their blood levels. More recent studies have been demonstrating that it is possible to control phe blood levels using BM as a phe source.⁶⁻⁹ The objective of this study was to evaluate the effect of BM as a phe source on the blood levels of this amino acid and on growth in children with PKU, compared with the traditional treatment.

Methods

A historic, prospective, paired cohort study was carried out. The sample was made up of 70 infants, 35 who had continued breastfeeding, born between January 2000 and April 2005, and accounting for 70% of the population diagnosed during that period, and 35 controls who were not breastfed, born between 1993 and 1999. All of the infants were screened by the PETN-MG and were being treated at the SEG-HC-UFMG. The breastfeeding group was composed of children who were being naturally breastfed on the day of diagnosis, had been born full term, with birth weight $\geq 2,500$ g, with no chronic diseases, and who started treatment by 40 days and continued breastfeeding up to at least 30 days after the start of therapy.

This group was compared to a control group, composed of 35 infants with PKU who had been given traditional treatment, paired for sex and age at breastfeeding cessation. These children were selected by lots from a list of possible controls who met the same inclusion criteria described above.

The variables of each pair were compared up to the age at which the child in the breastfeeding group ceased breastfeeding. After this point, the pair were no longer entered into analyses, and children were aged as close as possible to each other. Consultations and phe blood assays were carried out

weekly until 6 months of age and fortnightly thereafter up to 1 year.

The parents or guardians signed an informed consent form, and the study was approved by the Research Ethics Committee at the Universidade Federal de Minas Gerais (COEP-UFMG).

Until January of 2000, at the SEG-HC-UFMG all children with blood phe levels ≥ 10 mg/dL were treated using a commercial infant formula, given by bottle, and BM was withdrawn. From that point onwards, children that fulfilled the inclusion criteria were enrolled on the study, following a specific protocol. The treatment was based on research that has been published on the theme, which demonstrated that it was possible to continue breastfeeding while treating PKU.^{6-8,10}

Blood samples for assaying concentrations of the amino acid were taken by venous puncture, and phe assay was by ultramicrofluorometry, after elution.¹¹

The children in the breastfed group were given BM on demand during intervals between bottle feeds with "special formula", every 3 hours. The "special formula" was free from phe and contained protein substitute, water, carbohydrates and lipids. The calorie concentration of the "special formula" was kept at around 67 cal/100 mL. The volume of BM and the quantities of protein substitute and the other ingredients were defined according to blood phe levels, tested at each consultation, and which should be maintained within the range considered adequate for the first year of life.⁵

The method used to increase or reduce suckling at the breast and, consequently, to control phe intake, was to modify the volume and/or calorie concentration of the "special formula". The modifications were carried out in accordance with the following criteria:

- 1) If the phe assay was normal, then the volume and ingredients of the "special formula" were left unaltered.
- 2) If the phe assay result was > 6 mg/dL, then the "special formula" was altered, and the volume of each bottle feed was increased in the following manner: by 10 to 20 mL when phe was > 6 mg/dL and ≤ 8 mg/dL, by 20 to 40 mL when phe was > 8 mg/dL and ≤ 10 mg/dL, and by 40 to 50 mL when phe was > 10 mg/dL. In the event that phe assay results were > 6 mg/dL at three consecutive consultations, then BM would be withdrawn and traditional treatment started.
- 3) If the phe assay results were < 2 mg/dL, the volume and ingredients of the "special formula" for each bottle feed were reduced by 10 mL, in order to stimulate suckling at the breast and increase BM intake, until the phe levels reached recommended levels or until the volume of "special formula" reached a minimum of 20 mL/feed. If the volume reached this minimum, without increasing blood phe levels, for two consecutive consultations, then the calorie concentration of the "special formula" was

Table 1 - Comparison of the characteristics of the breastfed and control groups and the time (days) taken to normalize phe blood levels after starting treatment

	Breastfed group (n = 35)			Control group (n = 35)			p [†]
	P ₂₅	Median*	P ₇₅	P ₂₅	Median*	P ₇₅	
Birth weight (kg)	2.8	3.2 (2.6-4.2)	3.4	2.8	3.0 (2.5-3.9)	3.4	0.41
Blood phe at neonatal screening (mg/dL)	14.4	18.9 (5.3-45.3)	25.7	14.5	18.8 (6.0-48)	24.7	0.92
Blood phe at 1st consultation (mg/dL)	19.7	28.4 (11.5-47.9)	33.9	21.2	27.1 (11.8-48)	33.9	0.86
Age at screening test (days)	5	7 (4-25)	9	5	6 (4-19)	13	0.54
Age at 1st consultation (days)	19	23 (15-39)	26	21	24 (12-39)	33	0.08
Time (days) to normalize phe levels after starting treatment	7	8 (6-35)	14	7	7 (5-21)	14	0.47

p₂₅ = 25th percentile; p₇₅ = 75th percentile; phe = phenylalanine.

* Median (minimum-maximum).[†] Wilcoxon test for differences between medians.

reduced from 67 to 45 cal/100 mL. If blood phe levels continued at < 2 mg/dL, then commercial infant formula containing phe was added to the "special formula", whilst maintaining the BM.

The children in the control group were given milk-based commercial infant formula as their phe source, the amino acid profile of which is known. The "special formula" diet was prescribed for 24 hours, given in a bottle every 3 hours, and contained protein substitute, lipids and carbohydrates in addition to the commercial infant formula. At subsequent consultations, the quantity of commercial infant formula was altered depending on blood phe levels, while the concentration of the "special formula" was maintained at around 67 cal/mL.

For the breastfed group, the duration of breastfeeding was calculated and an analysis made of the number of children for whom it was necessary to introduce the commercial infant formula in order to maintain blood phe levels within recommended limits.

The characteristics of the two groups were compared using the Wilcoxon test, with the level of significance defined as $p < 0.05$.

The mean of blood phe assays results were analyzed, for both groups, throughout the period during which the children were being breastfed, with the exception of assays performed before starting treatment and on the day that the tolerance test was performed. The test is carried out at 6 months for diagnostic confirmation PKU classification.

Blood phe levels were grouped monthly at < 2 mg/dL; ≥ 2 mg/dL and ≤ 6 mg/dL and > 6 mg/dL for both breastfed and control groups.

The two groups were compared in terms of mean time (in days) to reach normal blood phe levels, using the Wilcoxon test, with the level of significance set at $p < 0.05$.

The nutritional status of the two groups was classified with the aid of Epi-Info (epinut), taking the z score ≥ -2 as the cut-off point between well-nourished and malnourished children. Measurements of the weight, stature and head circumference of each child were taken on the day of the first consultation and on the day, or the closest day possible to the day on which breastfeeding ceased. For the control group, the same measurements were also taken on the day of the first consultation and on the day corresponding to the age at which their pair had ceased BM. The anthropometric indices were compared with Student's paired t test using SPSS.

Results

Twenty-one (60%) of the 35 children in each group were male.

Table 1 contains the characteristics of the breastfed and control groups and a comparison of the time needed (in days, from the start of treatment) for their blood phe levels to reach the range of normality. It can be observed that there were no significant differences between the groups.

The mean duration of breastfeeding over the 12 months of follow-up was 224.4 ± 120.1 days, with a median of 199 days and a variation of 35 to 365 days. The numbers of children being breastfed, month by month, are illustrated in Figure 1.

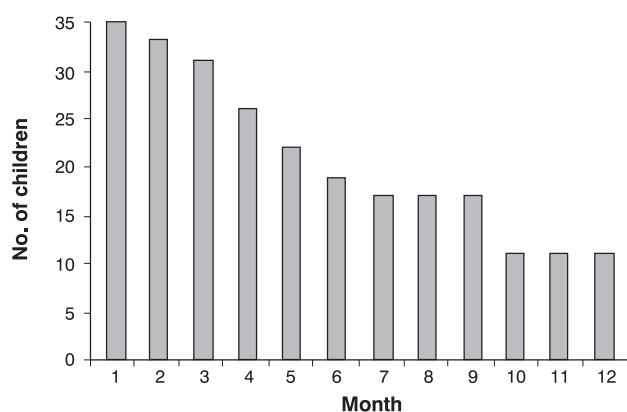
It was necessary to introduce commercial infant formula to the diets of 24 (68.5%) children, a mean of 75.4 ± 52 days after the start of treatment, in order to complete their phe intake, maintaining breastfeeding and levels of the amino acid in blood within recommended limits.

Figure 2 illustrates the means and standard deviations for the blood phe levels of each child in the breastfed and control groups over the study period, itself determined by duration of breastfeeding. Note that one child in the breastfed group and

Table 2 - Comparison of the breastfed and control groups in terms of the means of anthropometric indices, at first consultation and at the end of breastfeeding

Index	Group	Z score Mean ± SD	p*
Initial assessment			
Weight/stature (n = 30)	Breastfed	0.00±0.77	0.49
	Control	0.11±0.73	
Weight/age (n = 35)	Breastfed	-0.46±0.79	0.78
	Control	-0.51±0.72	
Stature/age (n = 35)	Breastfed	-0.77±0.74	0.68
	Control	-0.83±0.74	
Final assessment			
Weight/stature (n = 35)	Breastfed	0.11±0.90	0.72
	Control	0.19±0.86	
Weight/age (n = 35)	Breastfed	-0.14±0.99	0.19
	Control	0.13±0.95	
Stature/age (n = 35)	Breastfed	-0.29±1.01	0.24
	Control	-0.02±1.02	

SD = standard deviation.

* Student's *t* test.**Figure 1** - Distribution, month by month, of the number of children being breastfed over the 12 months of follow-up, after the start of treatment

two in the control group exhibited mean blood phe levels ≥ 6 mg/dL.

After analysis of the blood phe assays, we found that 30.9% of the 695 tests of children in the breastfed group were < 2 mg/dL, 56.1% were ≥ 2 mg/dL and ≤ 6 mg/dL and 13.8%

were > 6 mg/dL. In the control group, 34.9% of the 704 test results were < 2 mg/dL, 39.5% were ≤ 6 mg/dL and ≥ 2 mg/dL and 25.6% were > 6 mg/dL.

Table 2 contains a comparison of the two groups in terms of mean anthropometric indices at initial and final assessments. It was observed that there were no significant differences between any of the means of the anthropometric indices analyzed, either at start of treatment or at breastfeeding cessation, considering a 95% confidence level. At initial anthropometric assessment, one child in the breastfed group presented with a z score ≤ -2 for the weight/age and stature/age indices and another child did so for the stature/age index. In the control group, two children presented with a z score ≤ -2 : one for the weight/age index and the other for stature/age. At their final assessments, one of the breastfed children had a z score ≤ -2 for weight/stature and one other for stature/age; none of the children in the control group had a z score ≤ -2 .

The analysis of anthropometric follow-up (difference between final and initial assessments) for the breastfed and control groups demonstrated good progress in all indices in both groups; in the breastfed group, statistical significance was only detected in the difference in stature/age ratio ($p = 0.00$); in the control group statistical significance was detected in the change in stature/age ratio ($p = 0.00$) and the difference in weight/age ratio ($p = 0.00$).

On the day of the first consultation, mean head circumference in the breastfed group was 35.9 ± 1.4 cm and in the control group it was 36.1 ± 1.4 cm. There was no significant difference between the groups ($p = 0.7$). This analysis was based on 31 pairs of observations, as a result of a lack of measurements for some of the children in the control group.

At the final head circumference assessment, the breastfed group has a mean measurement of 44.0 ± 3.4 cm, and the control group mean was 44.0 ± 2.9 cm, once more with no significant difference between the groups ($p = 0.8$).

The evolution of head circumference, the difference between the final and initial measurements, was 7.9 ± 3.1 ($p = 0.0$) in the breastfed group. In the control group this difference was 7.7 ± 2.7 ($p = 0.0$). It will be observed that the children progressed favorably and that the difference was statistically significant for both groups.

Discussion

The possibility of maintaining natural breastfeeding as the source of phe in PKU treatment means that phenylketonuric infants can be offered all the advantages of BM, even if they are receiving it as part of a mixed breastfeeding. Among others, emphasis is due to the emotional advantages that the act of breastfeeding provides, both in strengthening the emotional bond between mother and child and in acceptance of disease.^{10,12} However, in order that the use of BM is effective for treatment of PKU, patients must attend frequent visits at

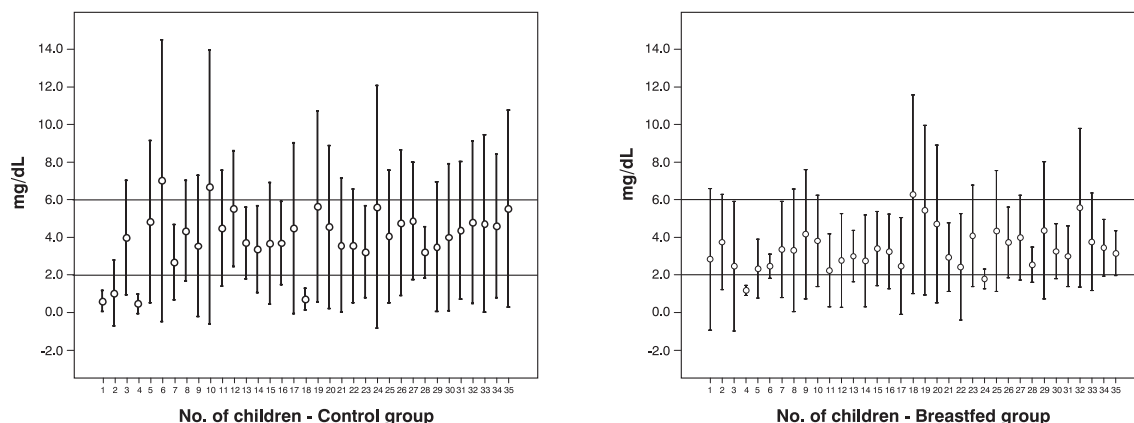


Figure 2 - Means and standard deviations of phenylalanine blood levels of each of the 35 children in the control and breast-fed groups, over the follow-up period

specialist centers, making possible constant dietary adjustments and adequate metabolic control, avoiding undesirable blood phe levels.^{6-9,13-15}

Even in the presence of certain risk factors for definitive weaning, which are inevitable in this situation, we consider that the breastfeeding duration of the children with PKU was very good and that it was comparable to the mean durations described in the literature, both for children with PKU and for Brazilian children without PKU.^{13,16,17} Demirkol et al.,¹³ McCabe et al.¹⁰ and Motzfeldt et al.⁶ found mean breastfeeding duration in phenylketonuric patients of 6.1, 8.9 and 7.0 months, respectively. However, in a study by Rijn et al.,⁷ breastfeeding duration was just 2.5 months. None of these authors make it clear whether their definition of breastfeeding duration included the period of breastfeeding before starting treatment. In our study this period was not included and, if it had been included in statistical analysis, we would have observed a longer mean breastfeeding duration than reported here. Although the breastfeeding duration of observed was below that recommended by the World Health Organization, one should take into account the fact that, when traditional treatment is used, children are definitively weaned during the first month of life. By maintaining BM in these phenylketonuric infants' diets, they benefit for a longer period which, according to the results of this study, can vary from 30 to 365 days after starting treatment.

The time needed from the start of treatment for blood phe levels to reach normal levels is very important. In this study we observed that the results of the two groups were statistically similar. Rijn et al.⁷ observed a mean time of 6 days for the amino acid to reach normal levels in the blood, in both groups. These authors assayed blood phe daily, and BM was given once a day, with feeds increased as phe levels reduced. Motzfeldt et al.⁶ reported a mean of 8 days for their patients' blood phe to reach normal levels and, in their study, BM was withdrawn for 1 to 3 days. We should point out that, in our

study, when calculating the time needed for blood phe levels to reach normal, a minimum period of 5 days after start of treatment was used, since the biochemical assays were performed weakly on the day of the consultation. Daily blood phe assays are not viable in developing countries, such as Brazil, because of the elevated cost of the procedure. The same explanation is applicable to the option of withdrawing BM temporarily, at the start of treatment, which has been performed in some studies, but which requires hospital admission.^{6,7} Our greatest initial concern when we implemented the use of BM for PKU was whether it would be possible to maintain blood levels within recommended limits. Analyzing of mean monthly ph blood measurements, during the period in which the children were being breastfed, we observed that for both groups, the majority of levels remained within the limits recommended by the literature.⁵ We also observed that the breastfed group exhibited less variability in terms of test results than the control group. When the blood phe levels of each child were analyzed, we observed a greater monthly proportion of normal test results in the breastfed group, when compared with the control group. This proportional analysis of blood phe levels was merely descriptive, since the number of tests for each child differed between groups, making statistical comparison impossible because of the likelihood of bias. Rijn et al.⁷ compared the proportions of blood phe levels between two groups, breastfed and control, and concluded that there was no statistical difference between them. However, the authors did not make it clear whether or not they compared an equal number of tests for the two groups. In our study, the majority of blood phe levels remained within limits considered safe throughout the period during which the children were being breastfed.

When we analyzed the pondero-statural growth of these children, we observed, in our statistics, that the majority of the children studied had a z score > -2, when the breastfed and control groups were compared, with no statistical difference between them. Analyzing the anthropometric evolution

of the breastfed group, we found that all of the indices assessed had improved, with statistical significance in the case of the stature/age index. Children in the control group also improved, although only the change in weight/stature ratio did not exhibit statistical significance. Head circumference grew at an appropriate rate, with significant progress and similar results for both groups. Maintaining breastfeeding while treating PKU made adequate growth possible during the breastfeeding period and the children developed in line with the reference standard for their age, confirming the findings of published literature.^{6-10,14}

Although the two groups were selected during distinct periods, we did not observe any implication of this that could have affected the research results. The protocol used at the SEG-HC-UFGM and the treating team were the same throughout the study.

We conclude that it is possible to use BM as the phe source in PKU treatment whilst maintaining adequate control of blood phe levels and keeping patient growth within normal limits. In the specific case of PKU, it should be added that, among all the benefits inherent to the conduct described here, that there is positive reinforcement of the mother-baby emotional bond, which has a positive impact on acceptance of the disease and compliance with treatment.

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