Case Report

Relato de Caso

Breastfeeding follow-up in the treatment of children with phenylketonuria

Acompanhamento do aleitamento materno no tratamento de crianças com fenilcetonúria

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Keywords

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ABSTRACT

Phenylketonuria (PKU) is the inability to convert phenylalanine into tyrosine, causing toxic effects to the central nervous system. Traditionally, in the treatment of PKU, breastfeeding is replaced by formula milk. This study verified the effects of breastfeeding as a source of phenylalanine on the development of children with PKU. Participants were ten infants with PKU who started treatment with the introduction of formula before 30 days of life, and maintained breastfeeding for at least 30 days after the start of procedures. The procedures were based on estimating breast milk intake, with a safe margin of phenylalanine concentration, calculating stomach volume, and initially offering formula, then breastfeeding on free demand, at every feeding. Breastfeeding duration ranged from one month and five days to 14 months. Blood controls were tested weekly. If the serum level of phenylalanine was >2 mg/dL and <6 mg/dL, the prescription was kept; if it was >2 mg/dL, the formula was decreased by 25%, indirectly increasing breastfeeding; if it was <6 mg/dL the formula was increased by 50%. The phenylalanine levels were assessed, and the Early Milestone Scale and the Basic Steps of Development were applied. Those who had normative index in all evaluations were considered adequate. Eighty percent of infants were able to keep safe concentrations of phenylalanine and development within normal indices. Continued breastfeeding is viable in the treatment of children with PKU, provided that phenylalanine levels are strictly controlled and the effects of breastfeeding on child development are monitored.

Descritores

Aleitamento materno
Fenilcetonúrias
Desenvolvimento infantil
Dietoterapia
Lactente
Metabolismo
Nutrição da criança

RESUMO

A fenilcetonúria (PKU) ocorre na incapacidade para transformar fenilalanina em tirosina, trazendo efeitos tóxicos para o sistema nervoso central. Tradicionalmente, no tratamento da PKU, o aleitamento materno é substituído por fórmula láctea. Este estudo verificou os efeitos do aleitamento materno como fonte de fenilalanina no desenvolvimento de crianças com PKU. Participaram dez lactentes com PKU, que iniciaram o tratamento com a introdução de fórmula láctea antes dos 30 dias e que mantiveram o aleitamento materno por no mínimo 30 dias de vida após o início dos procedimentos. Os procedimentos basearam-se em estimar a ingestão de leite materno, com margem segura da concentração da fenilalanina, calculando o volume gástrico e oferecendo inicialmente fórmula láctea, seguida do aleitamento materno em demanda livre, em todas as mamadas. O tempo de amamentação variou de um mês e cinco dias a 14 meses. Os controles sanguíneos foram semanais. Se o nível sérico da fenilalanina estivesse >2 mg/dL e <6 mg/dL mantinha-se a prescrição; se estivesse <2 mg/dL, diminuía-se a fórmula láctea em 25%, aumentando indiretamente o aleitamento materno; se estivesse >6 mg/dL, aumentava-se a fórmula em 50%. Avaliou-se os níveis de fenilalanina, aplicou-se a *Early Language Milestone* Scale e Passos Básicos do Desenvolvimento. Foram considerados adequados aqueles lactentes que apresentaram índices normativos em todas as avaliações. Dos lactentes, 80% conseguiram manter limites seguros da fenilalanina e desenvolvimento nos índices normativos. Há viabilidade da continuidade do aleitamento materno no tratamento de crianças com PKU desde que os níveis de fenilalanina sejam rigorosamente controlados e que os efeitos do aleitamento materno para o desenvolvimento infantil sejam verificados.

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INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive disorder resulting from the mutation of a gene located on chromosome 12q22-24.1. This metabolic failure is the inability to convert phenylalanine to tyrosine due to the absence of the enzyme that catalyzes this reaction, bringing toxic effects to the central nervous system (CNS). Phenylketonuria is irreversible, causing diffuse cerebral impairment[1,2]. Children not treated or who fail to maintain normal phenylalanine levels between >2 mg/dL and <6 mg/dL[3] in the first year of life may present progressive impairment of brain function and develop intellectual disability, hyperactivity, attention deficit disorder, seizures, delay in neurological and psychomotor development, and autistic behaviors[4,5].

Traditionally, in the treatment of PKU, breastfeeding (BF) is suspended and the phenylalanine needed is provided through commercial milk-based formula, which amino-acid concentration is known. The amount of formula is determined by blood phenylalanine levels and varies according to the tolerance of each individual to the intake of this amino-acid[5-7].

The suspension of BF would be necessary because of the difficulty to quantify the intake of phenylalanine during BF, which could cause a wide variation in blood levels and/or keep its concentration at levels above those recommended, incompatible with proper treatment[8-10] to prevent sequelae. For a long time breastfeeding babies recently diagnosed with PKU was considered not safe. However, mothers who had to abruptly stop breastfeeding their children after diagnosis experienced feelings of sadness and guilt, which interfered with the relationship with their babies and acceptance of diagnosis[9].

Phenylalanine is an essential amino-acid also for phenylketonuric patients and it should be included in their diet in the correct amount, allowing patients' development within the parameters of normality[1,4,6,7,10].

Dealing with BF is of extreme importance after PKU diagnosis[9]. Although breastfeeding in individuals with PKU is not common, there are advantages and disadvantages that must be carefully evaluated and individual tolerance must be accurately monitored.

Considering the accumulated studies on the benefits of BF[11-13] for children, from a biological and psychosocial point of view, this study aimed to investigate the effects of BF as a source of phenylalanine for child development and think over the importance of BF for this population.

CLINICAL CASES PRESENTATION

The project was approved by the Research Ethics Committee of the Bauru School of Dentistry, Universidade de São Paulo (USP), protocol number 088/2008. All the criteria of Resolution 196/96 were met. The parents or guardians signed an Informed Consent Form allowing the data contained in the medical records to be used in this study.

A total of ten infants with PKU screened by neonatal screening and diagnosed through blood tests, collected by venipuncture, participated in this study.

The following inclusion criteria were adopted to compose the sample: children with PKU, no chronic diseases, who started treatment with restricted intake of phenylalanine before 30 days of life and who kept BF for at least 30 days. The characterization of the sample by gender, level of phenylalanine at diagnosis, start of treatment with diet composed of BF and formula (mixed) and duration of BF are shown in Chart 1.

The mothers received weekly guidance on the importance of BF and the need to control plasma levels of phenylalanine to prevent deleterious effects on the CNS and their after effects on child development.

BF procedure was based on estimating the intake of breast milk in milligrams, according to age, with a safe margin of phenylalanine concentration, calculating stomach volume, and initially offering formula milk and then BF on free demand at every feeding.

Blood phenylalanine controls were performed weekly. The reference values of plasma phenylalanine in the first year of life are >2 mg/dL and <6 mg/dL[3]. The dosage of phenylalanine for blood level control during treatment with BF was performed through ultramicrofluorometry, after elution.

If the serum level of phenylalanine was between >2 mg/dL and <6 mg/dL the prescription was kept; if it was <2 mg/

Chart 1. Characterization of the sample

Participant	Gender	Phenylalanine mg/dL	Start of mixed diet	BF duration
P1	Female	10.4	8 days	4 months
P2	Female	22.0	10 days	4 months and 15 days
P3	Male	28.4	18 days	4 months
P4	Male	10.0	26 days	9 months
P5	Female	17.5	24 days	4 months and 20 days
P6	Male	38.2	18 days	4 months
P7	Male	16.5	23 days	1 month and 20 days
P8	Female	24.5	7 days	1 month and 5 days
P9	Male	10.4	14 days	6 months
P10	Male	26.8	30 days	14 months

Note: BF = breastfeeding

dL, formula milk was reduced by 25%, indirectly increasing BF; if it was >6 mg/dL formula milk was increased by 50%.

In the weekly follow-ups the levels of phenylalanine were assessed and the Early Language Milestone Scale[14] (ELM) and Basic Steps of Development[15] (BSD) were applied. The ELM scale assesses the auditory receptive, auditory expressive and visual functions. The BSD assesses the aspects of motor, cognitive, language and personal-social development. Infants who had normative indices in all evaluations were considered suitable as regards development.

The viability of keeping BF during treatment of children with PKU was verified by the minimum and maximum values, median and standard deviation (SD) of the results of blood phenylalanine levels, and by the results of development monitoring through ELM and PBD scales (Table 1).

Table 1. Minimum and maximum values, median, and standard deviation of blood phenylalanine levels and results from ELM and BSD

Participant	Minimum	Maximum	Median	SD	ELM/BSD
P1	2.2	10.4	4.6	3.8	A
P2	0.9	22.0	6.1	4.2	A
P3	1.6	28.4	7.6	7.8	I
P4	1.9	10.0	3.2	2.8	A
P5	2.1	17.5	3.5	3.5	A
P6	2.9	38.2	7.7	7.9	I
P7	2.0	16.5	5.4	5.3	A
P8	2.7	24.5	5.2	5.7	A
P9	1.5	10.4	4.5	2.5	A
P10	1.2	26.8	5.2	5.2	A

Note: SD = standard deviation; A = adequate; I = inadequate; ELM = Early Language Milestone Scale; BDS = Basic Steps of Development

DISCUSSION

Keeping BF in PKU, despite being a big challenge, is extremely important because there are advantages in BF that cannot be discarded[7-9,11-13]. BF offers a number of benefits from the biological and psychosocial perspective. Some of the benefits are the strengthening of the mother-baby emotional bond, the functional stimulation necessary for the maturation and neuromuscular development of the oral functions and nasal breathing that, together, will aid the growth and harmonious development of the stomatognathic and esthetic facial system[12,13].

During breastfeeding the child receives thermal, olfactory, visual, auditory and motor stimuli that favor their overall development, which is quite important for language development and for strengthening emotional relationships[11].

Among the main guidance received by mothers regarding BF is the importance of breastfeeding to protect against diseases[13]. However, in the case of children with PKU, these concepts must be reviewed, since BF must be controlled for these children because the intake of phenylalanine, with the change in metabolism, can cause variations in blood at levels incompatible with adequate treatment[8-10] to prevent sequels.

Studies[1,5,6] have shown that breast milk has low levels of phenylalanine compared to other infant formulas, however there is a need to check the metabolism of phenylketonuric babies, for if phenylalanine levels are high, there are risks for child development.

Moreover, BF in PKU[7-9] requires good guidance and mothers' commitment to meet the requirements of controlling phenylalanine levels through frequent blood tests. This is a big challenge and one of the factors interfering with breastfeeding duration. The reasons for BF discontinuation, such as return to work, stress, reduced breast milk production, among others, are no different from other reasons why mothers stop breastfeeding[9], with the addition, for families of phenylketonuric children, of the need to strictly control phenylalanine levels through frequent blood tests. In this study, the feeding time ranged from 1 month and five days to 14 months (Chart 1) and the feeding time prior to the start of procedures was not considered. One study[7] showed BF duration for phenylketonuric patients was only 2.5 months and another study[4] showed the duration ranged from 35 days to one year. Only the first study[7] reported that BF duration was considered after the start of procedures.

Although the number of participants in this study is small, results show that by applying the feeding protocol used, the concentration of phenylalanine could be maintained within safe levels. Other studies showed similar results[4,7,9]. Importantly, the analysis of the proportions of blood phenylalanine levels was merely descriptive, since the number of tests was different for each child. One study used similar criteria[7].

Table 1 shows that P3 and P6 had difficulty to control plasma levels in some samples, with median and standard deviation above 6 mg/dL. In these cases, the procedure was interrupted and the control was performed with exclusive use of infant formula and blood tests. Most of the other participants were able to maintain phenylalanine within safe limits.

One study[8] showed that 78% of PKU patients treated with BF and infant formula were able to maintain metabolic control at safe levels during the six month duration of the study. Metabolic control is also influenced by the genetic mutations on the mechanisms involving the level of phenylalanine in the blood[6-10], i.e. in PKU, combinations of genetic mutation may mean differences in phenylalanine tolerance and early metabolic control, which impacts the treatment. Hence the importance of frequent blood tests and genetic studies to understand these cases and manage the treatment of these individuals. Thus, there are children who, despite early diagnosis and treatment and strict diet control, cannot maintain plasma phenylalanine at safe levels and may have developmental disorders. It is noteworthy, however, that the neurological consequences of the biochemical effects may not only be linked to high levels of plasma phenylalanine, but also to other factors such as the effects of free amino-acids in the brain, the influence of dopamine and neurotransmitters and the effect of protein and myelin synthesis in the brain[2,3].

As for monitoring the development, P3 and P6 were out of the normal scales of development. The skills assessed in the experimental procedures were related to performance in motor, language and cognitive activities. Similar findings were found

in one study[6], in which 20% of the sample was also altered.

The metabolic disorder of phenylalanine interferes with cerebral protein synthesis, myelin formation and neurotransmitters, affecting particularly the dopaminergic pathways of the prefrontal cortex and can bring dysfunctions to the left hemisphere[5], particularly to the white matter, with effects on neuropsychological, language and learning functions[4,5].

Several studies showed that in phenylketonuric patients there is need for strict control of diet and phenylalanine levels, which should be well established in childhood[1,6-10].

PKU treatment is complex, long and requires behavioral changes from both patient and family for the prevention of developmental disorders, aiming their social, family and school integration. Treatment success, like in any chronic disease, depends on the willingness to follow the recommendations prescribed and should be part of an ongoing program throughout the life of the phenylketonuric individual.

FINAL COMMENTS

It is possible to keep BF during treatment of children with PKU providing phenylalanine levels are strictly controlled and BF effects on child development are monitored. In this study, 80% of infants were able to maintain phenylalanine within safe limits and development within normal indices. The other benefits that both the family and the child with PKU win with BF regarding physical, psychological and social aspects should be taken into account.

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