Evaluation of the program for prevention and health promotion in phenylketonuria patients in Brazil

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Abstract

Objective
To evaluate the results of systematizing preventive and health promotion actions among phenylketonuria (PKU) patients.

Methods
Results of phenylketonuria patients attended in the Prenatal PKU Screening Program in the State of Paraná, Brazil, from 1996 to 2001, were evaluated. Socioeconomic data were investigated and the gross motor function measure was applied to determine the motor score among 32 PKU infants with early diagnosis and treatment. Pearson's correlation coefficient was adopted to investigate the relationship between the target variable (motor score) and other quantitative variables (mean post-treatment serum phenylalanine level, parents' educational level, infant's age at the start of treatment, and family income).

Results
Among all the children evaluated, 93.7% showed development within normal limits as reported in the literature. Treatment was initiated in the first month of life in 71.9% of the PKU cases. Socioeconomic data showed 39.5% of parents having completed the fourth grade of primary school or less. There was a significant correlation between infant's motor score and parents' educational level (N=32), as well as between motor score and early treatment (N=27).

Conclusions
The results highlighted the program's effectiveness. The correlation between parents' low educational level and lower motor score emphasizes the importance of support for parents in their use of diet therapy. The association between motor score and early initiation of treatment confirms the need for immediate admission into the program. The paucity of other evaluation studies in the literature makes generalization of the results difficult.

INTRODUCTION

PKU is an autosomal recessive disorder resulting from the mutation of a gene located in chromosome 12q22-24.1,[7] causing liver deficiency of phenylalanine-hydroxylase, leading to reduced conversion of phenylalanine (PA) to tyrosine and a resulting increase in serum PA. Hyperphenylalaninemia (HPA), the generic term for increased serum PA, can be found in two different basic types: classical PKU with PA >10 mg/dl, and persistent hyperphenylalaninemia, with PA >4 mg/dl.[11]

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PKU is caused by the child's inability to use the amino acid phenylalanine. Early diagnosis and treatment of PA disorders are crucial to avoid brain damage and thus to prevent mental disability and motor and behavioral disorders, epilepsy, and stunting, among others.[5]

The reference plan for the limits between health and disease in PKU is basically identified by normal cognitive and motor development of the treated child. Early diagnosis is the first step, and diet therapy is initiated in the first weeks of life and extends throughout the lives of individuals with PKU. Many factors influence PKU treatment, and the encouragement of immediate and continuing diet adherence requires family support and an ongoing educational process, both for the parents and the health professionals dealing with the child. Various factors can lead to discontinuity of treatment: social pressures hindering social integration of individuals with PKU; financial constraints due to the high cost of special foods; lack of knowledge of PA levels in foods; lack of food products with reduced PA levels that meet nutritional needs; and lack of knowledge of the diet and its implications for the disease.

The results of a PKU treatment program hinge on multiple and complex interactions between the program's implementation (technology, training, materials, funding, and technical assistance) and institutional factors. Transparency of results as demonstrated by evaluation studies can be a facilitating factor for immediate treatment adherence in new cases.

According to Donabedian (1997),[3] an evaluation of the outcomes achieved by health services should reflect the effects of all health care inputs and can thus serve as an indicator for indirect quality evaluation of both the structure and the process.

The state of Paraná has been conducting neonatal screening for PKU and congenital hypothyroidism (HC) since 1987, where the neonatal screening program's main objective is early detection, allowing for timely treatment and follow-up of cases.

Blood samples obtained in maternity hospitals and wards statewide are referred to the FEPE's Research Center Laboratory (CEPE). Developed in partnership with the Unified National Health System (SUS), this initiative was the precursor for the screening program, which covers not only diagnosis but also treatment of PKU children. In 1996, FEPE set up a multidisciplinary team for diagnosis, laboratory follow-up, and treatment of these children.

The Paraná Association of PKU and Homocystinuria (HCU) Patients AFEH-PR was founded in 1992 to provide support to local PKU and HCU children and their parents. Based in the city of Curitiba, FEPE and AFEH-PR has created a link between the State and the community and are in charge of monitoring health of PKU patients.

The present study has the purpose of evaluating the results of systematizing preventive and health promotion activities for PKU patients.

METHODS

There were studied a total of 32 children treated early by the Paraná State Neonatal Screening Program from 1996 to 2001.

The Paraná program cares for 115 PKU patients, of whom 110 residing in Paraná and five in other states of Brazil (Santa Catarina and Mato Grosso). Of these, 42 were diagnosed at FEPE and began early treatment at the pioneering program of the Association of Parents and Friends of People with Mental Disabilities in São Paulo (APAE-SP). Of the 68 remaining cases, 33 late diagnosed and three early diagnosed cases were excluded from the study because they were older (aged 11, 13, and 14 years) than the rest of the group.

The group of 32 PKU children was selected according to the following criteria:

- Early diagnosis of PKU (up to 60 days after birth) or persistent hyperphenylalaninemia (HPA);
- Age from 0 to 6 years;
- Residence in the state of Paraná;
- Treatment at the FEPE in the capital Curitiba;
- Registered at the AFEH-PR, and
- Cases diagnosed by FEPE as of December 2001.

The study included 27 PKU children diagnosed up to 60 days after birth and 5 children with persistent HPA with early follow-up including clinical and laboratory tests during the pre-treatment period and who began treatment more than 60 days after birth.

The central focus of this evaluation was the analysis of the motor status of all selected cases. This analysis was performed using the gross motor function measure (GMFM), which allows for the determination of each patient's motor score, thereby facilitating diagnosis of the presence or absence of any delay or changes in motor development and the respective characteristics and intensity. The GMFM, a standardized observational instrument already validated and described in Canada, initially in 1990,[2] was reviewed in 1993 and 1994[10] and translated into Portuguese by Meyerhof and Gusman (2000).[8] The GMFM consists of 66 items

grouped in five different gross motor function dimensions: a) lie down and roll over; b) sit; c) crawl and kneel; d) stand, and e) walk, run, and jump. The target areas corresponding to the expected motor activity for each child's chronological age were based on motor behavior studies from 0 to 6 years by Eckert.[4]

A 10% variation was defined as the cutoff for within normal limits.[6]

The motor score was defined as an outcome measure of the FEPE state reference program in Curitiba. The following data were collected from patient files for analysis: diagnosis (PKU or persistent HPA); post-treatment serum PA; and age at start of treatment. A semi-structured interview was also conducted with the children's parents or guardian prior to the motor assessment. The interview was structured into questions concerning family's socioeconomic status, like income and parents' schooling. The study also attempted to record aspects that might enrich the data analysis on what facilitated or hindered treatment in each case. Quantitative data evaluation was conducted by analysis of simple frequencies using Epi Info 6.0.

Statistical analysis used the R and Statgraphics software programs. The variables are as follows:

Qualitative and dichotomous variable:
- Diagnosis: PKU or persistent HPA (which interferes with the determination of the start of treatment).

Quantitative variables:
- Motor score;
- Post-treatment serum PA;
- Family income;
- Age at start of treatment;
- Father's years of schooling; and
- Mother's years of schooling.

These variables were selected in order to investigate the possible factors influencing the results of diet therapy.

The Kolmogorov-Smirnov test was used for statistical analysis of data normalcy for each quantitative variable, and at a 5% significance level all variables showed a normal distribution. Thus it was chosen to adopt the Pearson's correlation coefficient and the relationship between the target variable (motor score) and other quantitative variables was evaluated.

This present study was conducted under authorization by the Research Ethics Committee at the Oswaldo Cruz Foundation/National School of Public Health, in accordance with Resolution 196/96 of the Brazilian National Health Council and related regulations.

RESULTS

Of 32 children studied, 16% live in the capital Curitiba and greater metropolitan area and 80% in other 21 cities of the state. The relatively small number of cases is distributed throughout the large territory of the state of Paraná.

Table 1 shows the prevalence of cases diagnosed and the coverage of heel prick tests. Only one screening test was considered for each newborn. While calculating the prevalence of diagnosed cases, it was included one case with late diagnosis (born in 1997 and starting treatment only in 1998), but other than the prevalence rate this case was not included in the rest of the data analysis for the group.

Motor scores in the 32 cases studied (PKU and persistent HPA) varied from 86.4 to 121.5. The data show only two cases (6.25%) with motor development below expected, as well as two cases (6.25%) with development above expected for their age. Considering a variation of 10%,[6] the vast majority of the cases (87.49%) presented gross motor function within nor-

Table 1 - Number of PKU cases, number of live births, PKU prevalence, number of heel prick tests performed, and respective population coverage, state of Paraná, Brazil, 1996–2001.

Year	PKU cases N	Live births* N	PKU prevalence	Heel prick tests** N	Population coverage %
1996	6	195,387	1: 32,564	169,970	86.99
1997	6***	192,220	1: 32,036	170,973	88.94
1998	4	185,113	1: 46,278	167,800	90.64
1999	6	186,105	1: 31,017	171,534	92.17
2000	9	178,194	1: 19,799	174,720	98.05
2001	1	166,971****	1: 166,971	165,318	99.01
Total	32	1,103,990	1: 34,499	1,020,315	92.42

Source: Number of PKU cases, Patient Registry, AFEH-PR (2002).[1]
*SESA / ISEP / CIDS (2002)
**FEPE Research Center (2002)
***One late case diagnosed in 1998
****Preliminary data from SESA

mal limits. Thus, 93.7% of the children presented satisfactory motor development for their age. One should emphasize that without adequate treatment, all these children would inevitably have developed severe motor and cognitive sequelae.

The motor score in the 5 cases of persistent HPA varied from 90.2 to 101.2, and the mean was lower than that for the total group of PKU children. The mean motor score for PKU children (98.71±1.97) differed from the mean motor score of children with persistent HPA (95.92±6.31). The difference between the mean scores was 2.79, and was not clinically significant.

Motor score results were correlated with the following quantitative variables: mean post-treatment serum PA, father's years of schooling, mother's years of schooling, age at start of treatment, and family income. This correlation is presented in Tables 2 through 6, respectively.

Table 2 shows the motor score distribution grouped in three developmental levels (low, medium, and high) according to mean post-treatment serum PA.

Mean post-treatment serum PA showed an optimal concentration (2-7 mg/dl) in 84.37% of the cases and a good concentration (below 10 mg/dl) in 12.5%. Also, it can be noted that two cases with low motor development level present higher serum PA levels.

The Pearson correlation coefficient (r) found in the association between motor score and mean post-treatment serum PA (mg/dl) was r=-0.0051. This shows a weak and inverse relationship between the variables, i.e., mean post-treatment serum PA had little influence on motor score results. This result was not statistically significant at a 5% significance level and a correlation coefficient p-value of 0.9788.

Table 3 shows motor score distribution according to father's schooling.

The Pearson's correlation coefficient in the association between motor score and father's educational level (years of schooling) was r=0.3512 and the correlation coefficient p-value was 0.0488. The statistical significance shows a weak and direct correlation between these two variables.

Table 4 shows motor score distribution according to mother's schooling. The distribution of these cases was similar to that found between motor score and father's schooling.

Table 2 - Motor score distribution according to mean post-treatment serum.

Serum PA (mg / dl)	Motor score Low		Medium		High		Total	
	N	%	N	%	N	%	N	%
3 a 4	-	-	6	21.4	-	-	6	18.75
4 a 5	-	-	3	10.7	-	-	3	9.37
5 a 6	-	-	8	28.6	1	50.0	9	28.13
6 a 7	1	50.0	6	21.4	1	50.0	8	25.0
7 a 9	1	50.0	3	10.7	-	-	4	12.5
9 or more	-	-	2	7.1	-	-	2	6.25
Total	2	100.0	28	100.0	2	100.0	32	100.0

PA: Phenylalanine

Table 3 - Motor score distribution by father's schooling.

Schooling	Motor score Low		Medium		High		Total	
	N	%	N	%	N	%	N	%
0 to 4th grades	2	100.0	10	35.71	-	-	12	37.5
5th to 8th grades	-	-	8	28.57	-	-	8	25.0
High school	-	-	9	32.14	1	50.0	10	31.25
University	-	-	1	3.58	1	50.0	2	6.25
Total	2	100.0	28	100.0	2	100.0	32	100.0

Table 4 - Motor score distribution by mother's schooling.

Schooling	Motor score Low		Medium		High		Total	
	N	%	N	%	N	%	N	%
0 to 4th grades	2	100.0	11	39.3	-	-	13	40.6
5th to 8th grades	-	-	11	39.3	1	50.0	12	37.5
High school	-	-	6	21.4	1	50.0	7	21.9
Total	2	100.0	28	100.0	2	100.0	32	100.0

The correlation coefficient found in the association between motor score and mother's schooling was r=0.3302. This shows a direct correlation between these variables, i.e., the greater the mother's schooling, the higher the motor score. This result was not found to be statistically significant, considering a 5% significance level and a correlation coefficient p-value of 0.065. However, the p-value is close to the established significance level.

Table 5 shows motor score distribution according to age at start of treatment. The cases of persistent HPA are those that began treatment more than 60 days after birth due to their lower serum PA levels.

To calculate this correlation, the five cases of persistent HPA that began treatment more 60 days after birth were grouped and it was carried out the analysis of motor score versus age at start of treatment in the 27 PKU cases that began treatment up to 60 days or less after birth.

The correlation coefficient in the association between motor score and age at start of treatment (in days) was r=-0.405, showing a weak and inverse correlation, i.e., the younger the child at start of treatment, the higher the motor score. Therefore, the earlier treatment is started, the better the motor performance in PKU children. This result was statistically significant at a 5% significance level and a correlation coefficient p-value of 0.03.

Table 6 shows motor score distribution by family income. According to socioeconomic data, the majority of families (90.6%) have a monthly family income of approximately U$ 340 (four times the Brazilian minimum wage) or less.

The correlation coefficient between motor score and family income was r=0.2134, showing a direct correlation between the variables; the greater the family income, the higher the motor score. This correlation was not statistically significant at a 5% significance level and a p-value of 0.2408.

DISCUSSION

PKU prevalence in Paraná in the study period, including five cases of persistent HPA, was approximately 1:34,500 live births, well below that reported in the literature. Elsewhere in Brazil, in the city of São Paulo, Schmidt et al[12] estimated a prevalence rate of 1:12,000 to 1:15,000 live births with PKU.[12] In Rio de Janeiro, estimated data in 1998 showed a total of 87,064 newborns tested, with 4 cases of classical PKU, i.e., a prevalence of 1: 21,766 live births.[9]

The population coverage of the heel prick test in newborns in the state of Paraná has increased steadily in recent years, from 86.99% in 1996 to 99.01% in 2001. National screening coverage is approximately 50% of all Brazilian neonates.[13]

When evaluating the results of the follow-up and treatment program for PKU children in the state of Paraná, there was found a 93.75% efficiency rate in cases with early treatment. The two children with low motor scores showed a critical condition in terms of the study variables: low monthly family income and father and mother with little or no schooling, besides having started treatment later. This fact hindered the analysis of each of the socioeconomic variables in the cases in which the program did not achieve good results.

In data analysis, no significant relationship was found between motor score and mean post-treatment

Table 5 - Motor score distribution by age at start of treatment.

Age at start of treatment	Motor score						Total	
	Low		Medium		High			
	N	%	N	%	N	%	N	%
8-30 days	-	-	21	75.0	2	100.0	23	71.87
31-60 days	2	100.0	2	7.1	-	-	4	12.5
>60 days	-	-	5	17.9	-	-	5	15.63
Total	2	100.0	28	100.0	2	100.0	32	100.0

Table 6 - Motor score distribution by family income.

Monthly family income (minimum wages - MW)	Motor score						Total	
	Low		Medium		High			
	N	%	N	%	N	%	N	%
0 to2 MW (U$ 0-165)	-	-	5	17.9	-	-	5	15.6
3 to 4 MW (U$ 195-340)	2	100.0	21	75.0	1	50.0	24	75.0
5 to 6 MW (U$ 425-510)	-	-	2	7.1	1	50.0	3	9.4
Total	2	100.0	28	100.0	2	100.0	32	100.0

MW: Brazilian minimum wage

PA. The diet is prescribed according to each child's metabolism, and serum PA concentration does not interfere directly in motor development when within therapeutic levels. Only one case with a below-average motor score presented a mean serum PA concentration of more than 10 mg/dl.

The challenge of achieving a balanced diet and filling out a food recall form requires that the child's caregivers be able of learning certain basic math operations. In the study it was observed a correlation (with a borderline significant p-value) between parents' schooling and child's motor performance. PKU children whose parents have more schooling tend to show better motor scores. In the present series, 39.1% of the parents have less than four years of schooling. Thus, the program's team should continue to focus on orienting and supporting parents who have less schooling.

In 71.9% of the cases studied, treatment started within the first month of life. The correlation between motor score and start of treatment clearly shows that an efficient PKU program requires active case search and a focus on immediate treatment adherence. It is crucial to have an integrated, complex and multidisciplinary system in place in order to handle cases in timely fashion.[13]

There was no significant relationship between motor score and family income in the cases studied. This reveals the efficiency of the support provided to low-income families served by the program, a basic condition for prevention and health promotion measures to be developed successfully due to the high cost of diet therapy.

The results of screening programs conducted by professionals who are not part of the treatment team need to be evaluated. Evaluation of motor development contributed to the identification of the results of nutritional treatment, especially in younger infants, in whom more specific psychomotor tests are more difficult to perform.

The lack of other similar evaluation studies in the literature hampers the generalization and comparison of data. It is important to conduct other such studies that evaluate and disseminate the results of public neonatal screening programs. Transparency of results can increase the programs' credibility and foster immediate treatment adherence. This is particularly important in the case of PKU children.

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