

Adherence to Treatment of Phenylketonuria: A Study in Southern Brazilian Patients

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Abstract

Introduction: Phenylketonuria (PKU) is caused by the deficient activity of phenylalanine hydroxylase. **Aim:** To identify the factors associated with treatment adherence among patients with PKU seen at a southern Brazil reference center. **Methodology:** A cross-sectional, outpatient-based study including 56 patients with PKU (median age, 12 years) for whom a Phe-restrict diet plus specific metabolic formula have been prescribed. Patients were considered adherent or nonadherent depending on the median phenylalanine concentration for the 12 months prior to study and target levels of phenylalanine for each age range (<13 years = ≤ 360 $\mu\text{mol/L}$; ≥ 13 years = ≤ 900 $\mu\text{mol/L}$). Data were collected through a review of patient's medical records and a set of interviews with patients and their relatives. **Results:** Eighteen patients (32.1%; ≥ 13 years, 11) were classified as treatment adherent. Among all factors analyzed, only mental retardation, living with parents, and level of maternal education were associated with adherence to treatment. **Conclusion:** Our findings reinforce the importance of the family as promoting factor for treatment adherence.

Keywords

phenylketonuria, adherence to treatment, inborn errors of metabolism

Introduction

Phenylketonuria (PKU; OMIM 261600) is an inborn error of metabolism caused by the deficient activity of the enzyme phenylalanine hydroxylase (EC1.14.16.1), which catalyzes conversion of the amino acid phenylalanine (Phe) into tyrosine. Consequently, patients develop elevated serum concentration of Phe, which is toxic to the central nervous system. Currently, most cases of PKU are diagnosed through neonatal screening programs.¹ Screening of PKU usually consists of measurement of Phe concentration in blood spotted on filter paper, preferably between the third and the seventh day of life.^{2,3}

Management of PKU consists of a Phe-restricted diet—including the use of a specific metabolic formula (MF) containing amino acids and micronutrients, but free of Phe—adjusted individually according to target Phe levels for each age range,⁴ which should usually be followed throughout the patient's life.⁵ With early diagnosis and treatment, patients are practically asymptomatic.¹ In untreated patients, the most common clinical manifestation is mental retardation; hyperactivity, autism,

pyramidal tract signs, tremor, seizures, and microcephaly are also common.^{1,6}

Adherence to PKU dietary treatment is usually estimated by comparing the patient's serum Phe concentration with target levels recommended in the literature.⁴ In many chronic

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conditions, treatment adherence decreases over time, and the finding that Phe concentration increases with age shows that PKU is no exception.⁷ This may be due to poor understanding of dietary restrictions, decreased motivation to comply with treatment, and inability to cope with the disease. Adherence to PKU treatment may also be influenced by factors such as education, religion, socioeconomic circumstances—such as access to specific products for management of PKU, family income, and housing conditions—and also by the patient's relationship with and trust in his or her team of health care providers.^{7,8} Patients with separated or divorced parents, for instance, may have higher Phe levels.⁹ This study sought to identify the factors associated with treatment adherence in patients with PKU seen at a reference center in Southern Brazil.

Methods

The present study employed a cross-sectional, outpatient-based design and was approved by the local Research Ethics Committee. After informed consent forms had been signed, all necessary information was obtained through a review of patients' medical records and interviews with patients and their relatives. Data were collected over a 12-month period.

The study sample included patients with a diagnosis of PKU followed up at Medical Genetics Service-Hospital de Clínicas de Porto Alegre/Brazil outpatient PKU clinic. The PKU clinic, which has been operating since 1991, has a multidisciplinary team (consisting of physicians, a dietitian, a social worker, a psychologist, and several undergraduate and graduate students of health-related programs) and currently includes 65 patients—approximately half of the patients with PKU currently being treated for the condition in the state of Rio Grande do Sul, Brazil. Patients in the first year of life are seen at the clinic at least every month, those aged 1 to 18 years have appointments at least every 3 months, and adult patients are seen at least twice a year. Of the 65 patients, 4 presented off-diet values of Phe <360 $\mu\text{mol/L}$ and did not need any dietary intervention; therefore, they were not included in the study. As 5 patients declined to be included, 56 patients composed the total sample.

Classification of PKU phenotype was based on serum concentration of Phe at diagnosis (before treatment); patients with Phe levels $\geq 1200 \mu\text{mol/L}$ were classified as having classical PKU, and those with Phe levels between 360 and 1200 $\mu\text{mol/L}$ were classified as having mild PKU. Patients for whom data on Phe levels at diagnosis were unavailable were classified as having "PKU of undefined type."¹⁰

Patients were classified as treatment adherent or nonadherent according to the comparison between the median Phe levels over the past 12 months of follow-up and the target Phe concentration adopted in the clinic⁴ as well as to the number of Phe measurements performed in the period. Patients younger than 18 years who underwent fewer than 3 Phe measurements over the 12-month follow-up period were considered nonadherent to treatment, regardless of median Phe level; adult patients required at least 2 yearly Phe

measurements to be considered adherent. Patients under the age of 13 were required to have serum Phe levels of $\leq 360 \mu\text{mol/L}$ (target value for this age range), and those 13 or older were required to have a median Phe level of $\leq 900 \mu\text{mol/L}$ (target value for this age range). The presence/absence of mental retardation was acknowledged according to the assistant physician's opinion as noted in each patient's records; no IQ tests were available.

Questionnaires

Three questionnaires (I, II, and III) devised by the PKU clinic multidisciplinary team, mostly comprising multiple-choice questions, were administered to patients and/or their relatives. These questionnaires are available as a supplementary material.

Questionnaire I was administered only to patients aged 12 or older (or, when the patient's cognitive abilities were insufficient to allow completion, to his or her parents) and contained questions on family history and socioeconomic conditions, educational level, intrafamilial variability, and access to the MF.

Questionnaires II and III comprised 12 questions each meant to assess the understanding of PKU (8 questions), the description of the PKU diet (2 questions), and main challenges to treatment adherence (2 questions). Questionnaire II should be answered by the main caretaker of patients aged younger than 12 years or of patients presenting neurological compromise, while questionnaire III should be answered by patients aged 12 or older when cognitive ability allowed. Knowledge about PKU was classified according to the answers provided to the 8 questions aiming at evaluating it (1 point was given to each correct answer): satisfactory (7-8 points), fair (4-6 points), and unsatisfactory (<4 points).

Statistical Analysis

Statistical analysis was carried out using SPSS for Windows, version 18.0 (SPSS Inc, Chicago, Illinois). Continuous variables were expressed as mean \pm standard deviation or median and interquartile range. The chi-square and Fisher exact tests were used to test for association between categorical variables. Adjustment for confounding factors was accomplished with the use of Poisson regression to test for association between variables. The Mann-Whitney *U* test was used for comparison of independent samples. Correlation between parameters was assessed with Spearman correlation coefficient. The level of significance was $P < .05$.

Results

Of the 56 patients included (Table 1), 31 were aged 0 to 13 years, 13 were aged 13 to 18 years, and 12 were older than 18 years. Median age at inclusion was 12 years (interquartile range, 9-17 years; range, 0-56 years), and at diagnosis, 2 months (interquartile range, 1-19.2 months; range, 0.6-137 months). Forty-nine patients had been born to unrelated families, and consanguinity was present in 10 (20.4%) of 49 families. As for

Table 1. Demographic and Social Characteristics of Patients With Phenylketonuria According to Their Treatment Adherence.^a

Characteristics	Adherent (n = 18), n (%)	Nonadherent (n = 38), n (%)	P
Age at inclusion (n = 56)			.088 ^b
≥ 13 years	11 (44.0)	14 (56.0)	
<13 years	7 (22.6)	24 (77.4)	
Gender (n = 56)			.579 ^b
Male	9 (29.0)	22 (71.0)	
Female	9 (36.0)	16 (64.0)	
Origin (n = 56)			1.000 ^c
Rural area	2 (33.3)	4 (66.7)	
Urban area	16 (32.0)	34 (68.0)	
Housing (n = 56)			.759 ^c
Owned	16 (34.8)	30 (65.2)	
Rented	1 (20.0)	4 (80.0)	
Shared	1 (20.0)	4 (80.0)	
Maternal educational achievement (in years of schooling; n = 55) ^d			.899 ^c
4 years or less	5 (33.3)	10 (66.7)	
5 to 8 years	5 (29.4)	12 (70.6)	
9 to 12 years	6 (31.6)	13 (68.4)	
>12 years	2 (50.0)	2 (50.0)	
Paternal educational achievement (in years of schooling; n = 52) ^e			.695 ^c
4 years or less	5 (26.3)	14 (73.7)	
5-8 years	3 (27.3)	8 (72.7)	
9-12 years	8 (44.4)	10 (55.6)	
>12 years	1 (25.0)	3 (75.0)	
Patients' educational achievement (in years of schooling; n = 56)			.667 ^c
0-4 years	6 (26.1)	17 (73.9)	
5-8 years	5 (31.3)	11 (68.8)	
9-12 years	3 (50.0)	3 (50.0)	
Special education	4 (36.4)	7 (63.6)	
Economic class ^f (n = 50)			.500 ^c
Class B	9 (37.5)	15 (62.5)	
Class C	6 (25.0)	18 (75.0)	
Class D	1 (50.0)	1 (50.0)	

^an = 56.^bChi-square test.^cFisher exact test.^dOne patient did not answer the question on maternal educational achievement.^eFour patients did not answer the question on the paternal educational achievement.^fEconomic class was established according to the Brazilian Economic Classification Criterion developed by the Brazilian Association of Research Companies (Associação Nacional de Empresas de Pesquisa), which uses acquisition of consumer goods (as a surrogate for family purchasing power) and educational achievement of the head of household. No families could be classified into class A. Six families were not classified, as they did not answer the questions meant to assess economic status.

PKU phenotype, 32 patients (58.9%) were classified as having classical PKU and 17 (28.6%) as having mild PKU; disease subtype was undefined in the 7 remaining patients.

Regarding adherence to treatment, 18 (32.1%) patients were considered adherent (median current age, 13 years; interquartile

range, 7.7-17), with a median age at diagnosis of 3.0 months (interquartile range, 1.54-13.25; only 4 [22.2%] patients were diagnosed through newborn screening). Thirty-eight patients were considered nonadherent (median current age, 11.5 years; interquartile range, 9-18), with a median age at diagnosis of 2.0 months (interquartile range, 1.38-2; only 8 [21%] patients were diagnosed through newborn screening; Table 1).

There was no difference in frequency of clinical manifestations between the adherent and the nonadherent groups (data not shown). Mental retardation was the most common clinical manifestation found (Table 2).

The association between clinical manifestations of PKU and age at diagnosis, and with median serum Phe concentration in the first 12 months after diagnosis, showed that the later the diagnosis, the higher the risk of mental retardation and that the higher the concentration of Phe, the higher the risk of mental retardation, hyperactivity, and seizures (Table 2). The same analysis was performed on median Phe concentration for the 12 months preceding the inclusion in the study; the only significant association was with mental retardation (risk ratio [RR] 1.19, 95% confidence interval [CI] 1.03-1.20, $p = 0.004$).

Demographic and Social Characteristics

A summary of demographic and social characteristics of the study sample according to treatment adherence is shown in Table 1. Patients whose mothers had a lower educational level—namely, less than 4 years of formal education—were at a greater risk of treatment nonadherence. Adjusted analysis of the association between sociodemographic characteristics and treatment adherence showed an association between educational achievement and adherence; patients whose mothers had 4 years of formal education or less were at greater risk of nonadherence (RR 1.59, 95% CI 1.01-2.51, $P = .044$).

Origin

Mean distance between patient residence and the PKU clinic was 329.57 ± 95.45 km. Among nonadherent patients living in the countryside (n = 22), mean distance was 118.13 ± 193.08 km versus 207.06 ± 208.60 km in the treatment-adherent group living in the countryside (n = 11; $P = .792$). Also, the distance between the patient's town of origin and the PKU clinic did not correlate with median Phe concentration in the 12 months prior to study inclusion (adherent patients, n = 18, $r = -.12$, $P = .629$; nonadherent patients, n = 34, $r = .06$, $P = .72$).

Living With Relatives

Most patients (n = 38 of 55, 69.1%) lived with both parents; of these, 22 (57.9%) did not adhere to treatment. Among patients who lived with only one parent (n = 17/55, 30.9%), 15 (27.3%) were nonadherent ($P = .027$). Adjusted analysis of this variable revealed that living with both parents is a protective factor for treatment adherence (RRs 0.59, 95% CI 0.39-0.80, $P = .001$).

Table 2. Clinical Manifestations of Phenylketonuria and Their Association With Age at Diagnosis and With the Phenylalanine Concentration in the First 12 Months of Follow-Up.^a

	Median Phe in the First 12 Months			Age at Diagnosis		
	RR	CI (95%)	P ^b	RR	CI (95%)	P ^b
Mental retardation (n = 21)	1.066	1.024-1.111	.002	1.005	1.001-1.009	.006
Learning disability (n = 18)	1.063	0.978-1.155	.149	0.990	0.979-1.002	.103
Hyperactivity (n = 9)	1.174	1.070-1.289	.001	0.989	0.977-1.101	.079
Microcephaly (n = 8)	0.870	0.727-1.042	.130	1.012	0.995-1.028	.169
Seizures (n = 8)	1.151	1.017-1.303	.026	0.988	0.974-1.002	.087
Low weight (n = 7)	0.885	0.744-1.053	.169	1.014	0.999-1.029	.066
Short stature (n = 6)	0.935	0.760-1.151	.526	1.013	0.999-1.027	.080
Aggressiveness (n = 6)	1.082	0.978-1.196	.125	1.004	0.992-1.016	.509
Attention deficit (n = 4)	1.240	1.009-1.523	.041	0.982	0.957-1.008	.170

Abbreviations: RR, relative risk; CI, confidence interval.

^an = 48.

^bPoisson regression.

Table 3. A Clinical Summary of Patients With Phenylketonuria Included in this Study Who Are Siblings.^a

Family/Patient	Current Age, yr	Gender	Adherence to Treatment	Early/Late Diagnosis	Knowledge of PKU ^b
A1	10	Male	No	Early	Fair
A2	14	Male	Yes	Early	Fair
B1	09	Male	No	Early	Fair
B2	14	Female	No	Late	Fair
B3	17	Male	Yes	Late	Unsatisfactory
C1	17	Female	Yes	Late	Unsatisfactory
C2	21	Male	No	Late	Fair
D1	8	Male	No	Late	Fair
D2	14	Male	Yes	Late	Satisfactory

Abbreviation: PKU, phenylketonuria.

^an = 9 patients from 4 families.

^bAccording to the questionnaire devised for this research: satisfactory (7-8 points), fair (4-6 points), and unsatisfactory (<4 points).

This variable was not assessed in one patient who lived alone. There was no significant difference in treatment adherence between patients who have siblings and those who did not ($P = .394$).

Intrafamilial Variability

Of the siblings included in the study (n = 16, from 4 families), 9 diverged in compliance (from families A, B, C, and D) and are described in Table 3.

Knowledge of PKU

The questions related to knowledge of PKU were answered by 37 caretakers (questionnaire II) and by 19 patients (questionnaire III). Since we had one questionnaire per patient, we analyzed both questionnaires together. In the treatment-adherent group (n = 18 of 56), 9 (50%) questionnaires showed that the respondent had satisfactory knowledge of PKU, 6 (33.3%) showed that the respondent had fair knowledge of the condition, and 3 (16.7%) showed that the respondent had an unsatisfactory understanding of the disease. In the nonadherent group

(n = 38 of 56), these numbers were 14 (41.8%), 20 (54.1%), and 3 (8.1%), respectively. There was no significant difference in knowledge of PKU between the adherent and the nonadherent groups ($P = .297$) and no association between median Phe concentration in the last 12 months and knowledge of the condition ($r = .181$, $P = .311$).

Diet

Forty-seven patients claimed to always use MF as directed by the clinical dietitian. Three patients used it as recommended only occasionally and one never did; 6 patients failed to answer the question. In the nonadherent group, 31 patients claimed to always follow recommendations regarding use of MF versus 16 patients in the adherent group ($P = .686$). Patients were then asked about MF supply in the 12 months prior to interview. Of the 54 patients or family members who answered the question, only 4 (7.4%) claimed to have received it on a regular basis during the period. One patient did not use MF at all and one failed to answer the question. Analysis of MF supply and median Phe levels over the 12 months prior to study showed that, in the group of patients who received the formula

Table 4. Reported Frequency of Challenges Associated With Treatment of Phenylketonuria.

	Adherent (n = 17/18), %	Nonadherent (n = 36/38), %	P
Dietary restrictions	12 (70.5)	24 (66.6)	.775 ^a
Palatability of MF ^b	10 (58.8)	23 (63.8)	.723 ^a
MF ^b supply issues	10 (58.8)	23 (63.8)	.723 ^a
High cost of MF ^b	9 (52.9)	18 (50.0)	.842 ^a
Distance to the PKU clinic	8 (47.1)	18 (50.0)	.842 ^a
Cost of transportation to the PKU clinic	5 (29.4)	11 (30.5)	.933 ^a
Impaired social interaction with non-PKU patients	4 (23.5)	8 (22.2)	1.000 ^c
High cost of other PKU-diet foods	2 (11.8)	1 (2.8)	.238 ^a

Abbreviations: PKU, phenylketonuria; MF, metabolic formula.

^aChi-square test.

^bMF is funded and supplied by each state's Department of Health.

^cFisher exact test.

regularly (n = 4), median Phe level was 581.18 μmol/L (interquartile range, 363.2-684.1) versus 659.8 μmol/L (interquartile range, 169.5-1174.4) in patients who reported not receiving it on a regular basis (P = .450).

Treatment Challenges

The questions related to treatment challenges were answered by 37 caretakers (questionnaire II) and by 16 patients (questionnaire III). Since we had one questionnaire per patient, we analyzed both questionnaires together. Table 4 shows the reported frequency of challenges or difficulties associated with PKU treatment.

Only one caretaker claimed to have no difficulty in adhering to treatment. When asked whether PKU was in any way a nuisance in their lives, 8 (50.0%) of the 16 patients who answered questionnaire III replied in the affirmative. Of these 8, 3 claimed that eating out was a nuisance, one reported out-of-town follow-up as an issue, 3 complained of dietary restrictions, and one reported forgetfulness, which interfered with treatment adherence.

Discussion

In Brazil, PKU was the first condition to be included in a neonatal screening program in the 1970s; however, the first specific program establishing a nationwide screening network—the National Neonatal Screening Program (Programa Nacional de Triagem Neonatal)—was only established in 2001.² Phenylalanine-free MF is made available as a PKU treatment through the Brazilian Ministry of Health's Specialized Program for Pharmaceutical Assistance (Componente Especializado da Assistência Farmacêutica) and is thus state funded.¹¹

A high level of treatment nonadherence was found in the present study. We used number of Phe measurements and median blood Phe concentration in the 12 months prior to study inclusion when compared to target levels as parameters for

adherence assessment. These parameters are recommended as a direct and reliable measurement of adherence.¹² Adherence to PKU treatment is difficult to quantify and has been the subject of few studies; there is no single measurement to assess it, and other parameters are used as well, such as dietary recall, MF consumption, and self-reported compliance in interviews with health professionals.^{13,14}

Both groups (adherent and not adherent) did not differ regarding the proportion of early (eg, through newborn screening) and late diagnosed patients and the presence of mental retardation. However, as expected, we found out a higher risk of mental retardation among individuals presenting higher concentrations of Phe after the first 12 months of follow-up and later ages at diagnosis as well, findings which reinforce the importance of neonatal screening for this disease. As higher Phe concentrations in the 12 months before the inclusion in the study were also associated with the occurrence of mental retardation, our findings suggest mental retardation indeed negatively affects adherence to treatment.

Regarding patient origin and distance to the PKU clinic, most patients lived in the countryside, and although distance and transportation cost were reported as challenges associated with PKU treatment, there was no association between adherence and distance. This finding may be due to the fact that free transportation to the PKU clinic is made available to patients who live in other municipalities by their municipal governments and because the MF is provided to patients at their municipalities of origin. A study conducted at Colorado University also showed that geographic access to care does not impact adherence to PKU treatment and control of Phe concentration.¹⁵

The present study showed an association between treatment adherence and living with both parents; patients who did not live with both parents were therefore more likely to have higher Phe levels. A prior study conducted in Sweden found that children of divorced parents were more likely to have high Phe concentration, as found in the present study, showing that coping strategies for PKU must be viewed within a family relations context.⁹ Another study conducted in Iran also showed that there was a significant increase in Phe concentration among patients whose parents were divorced.¹⁶

Parental knowledge of PKU is absolutely essential for proper treatment and control,⁵ and the quality of control depends on parental ability to and discipline in implementing and supervising an appropriate diet.⁷ In our study, most patients and/or caretakers were found to have satisfactory and fair knowledge of PKU.

A study conducted in England tested maternal knowledge and found that the higher the score of mothers of patients with PKU, the better their annual Phe control and that the mothers of patients with higher Phe concentration tended to have lower educational achievement.⁷ In the present study, we indeed found an association between maternal educational achievement and treatment adherence, with patients whose mothers had lower levels of formal education being at greater risk of nonadherence.

In chronic diseases such as PKU, treatment adherence tends to decrease over time, and serum Phe concentration exceeds target limits, especially in adolescents and adults.^{17,18} In the present study, most adherent patients were older than 13 years, a finding that is unexpected according to the literature. This may be explained by our choice of 900 $\mu\text{mol/L}$ as the upper target for Phe levels in this age range. A recent study conducted in European centers, however, suggests that adherence is improving in adolescent and adult patients.¹⁴

Difficulty in living with an invisible (and possibly socially unaccepted) condition, coupled with the dearth of studies assessing the social effects of the lifestyle limitations and dietary restrictions of PKU, may be directly associated with treatment adherence.^{5,13} We found dietary restriction to be one of the challenges most frequently reported by the patients and family members interviewed in this study, as was obtaining an adequate supply of MF, which is a key component of PKU treatment. Identifying factors associated with dietary adherence, assessing knowledge of therapeutic regimen and treatment, and highlighting the importance of family relations in maintaining adherence to an appropriate diet play an essential role in supporting families and making treatment more effective. Interventions such as home visits, educational materials, games, courses, and cooking classes in which the food issue is given due importance have all been described as having positive effects on adherence to PKU treatment.^{5,7,19,20}

Our data confirm that siblings can show variability in treatment adherence. Although our sample of siblings is small, it does not suggest that there is an association between gender, early/late diagnosis, and knowledge of PKU. However, an association appears to exist between current age and adherence (the older the patient, the better the adherence)—of the 4 families assessed, the adherent patient was the older one in 3, a fact that may be explained by the cutoffs adopted to classify treatment adherence according to patient's age.

One of the limitations of our study was the absence of more diversified questions for assessing knowledge of PKU. In future studies, we intend to assess family stance on religion, which was not addressed at the present time, and factors associated with intrafamilial variability in adherence. Other limitation was the broad heterogeneity of sample's age, since the oldest patients have actually been treated since times when objectives and circumstances were different. These changes (Phe target level, frequency of controls, health staff, and treatment out of an organized screening program) must influence the adherence and have not been analyzed in our study.

We conclude that the issue of adherence to PKU treatment still requires further studies and that the challenges associated with PKU treatment should be discussed and addressed jointly by families and health professionals so that the most effective interventions can be identified for each case. As this was the first study of its kind to be carried out on a sample of Brazilian patients with PKU, we hope its findings can contribute to improve treatment adherence and quality of

life in this population. We suggest all nonadherent patients should be periodically reevaluated in order to identify the reasons for nonadherence and to improve the educational and nutritional skills of the family.

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Declaration of Conflicting Interests

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Supplemental Material

The online data supplements are available at <http://iem.sagepub.com/supplemental>.

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