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Treatment adherence during childhood in individuals with phenylketonuria: Early signs of treatment discontinuation

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ABSTRACT

Introduction: Phenylketonuria (PKU) is an autosomal recessive disorder characterized by a deficiency in phenylalanine (Phe) hydroxylase activity. Early diagnosis and continuous treatment with a low Phe diet prevents severe neurological and cognitive impairment.
Aims: 1. Analyze how treatment adherence evolves through infancy, childhood, and early adolescence in individuals with PKU. 2. Identify early signs of treatment discontinuation.
Methodology: This longitudinal, retrospective study included 75 children diagnosed through newborn screening, ages 7 to 13 years. Data on blood Phe concentration, number of blood samples sent, proportion of samples with Phe concentrations over the recommended range, and number of visits to the metabolism clinic were recorded. Logistic regression analysis was used to identify the variables that predict treatment discontinuation before 13 years of age.
Results: A progressive increase in mean blood Phe concentrations with age was identified. The greatest increase occurred between the first and second years of life. By age ten, mean Phe blood concentration of the group was above the recommended range. The proportion of samples with Phe concentrations over the recommended range also increased with age, from an average of 13% during the first year of life to 67% in early adolescence. Sixty-eight percent of the children attended the outpatient clinic and sent samples from birth to the time of the study. Individuals who discontinued follow-up showed significantly higher mean blood Phe concentrations (360 vs. 220.9 μmol/L; $p = 0.004$) and the proportion of samples over the recommended range (37% vs. 12% $p = 0.002$) was significantly higher during the second year of life. Mean age for children who discontinued treatment was 5.5 years of age. Blood Phe concentration values at 12 to 23 months of age and at 6 to 8 years of age significantly predicted treatment discontinuation before 13 years of age.
Conclusion: Treatment adherence in PKU diminishes with age. Early signs of treatment discontinuation can be identified during the second year of life, allowing preventive interventions in high risk groups.

1. Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder characterized by a deficiency in phenylalanine hydroxylase activity, causing increased phenylalanine (Phe) plasma and tissue concentrations. Left untreated, PKU leads to severe intellectual disability. Early diagnosis and continuous treatment with a low Phe diet prevents severe neurological and cognitive impairment in affected individuals, with the achievement of intelligence quotients (IQs) within the average range, but lower than control groups [1–7].

Treatment for PKU requires avoidance of high protein foods, such as all meats, dairy, nuts, beans, and eggs and allows for only measured amounts of grains, fruits, and vegetables. A special formula provides the necessary nutrients found in protein without the phenylalanine. The diet is extremely restrictive and the formula has a strong taste and odor, which makes adherence to treatment extremely challenging [8,9].

In a study of treatment adherence in 56 Brazilian PKU patients, in which adherence was defined by the median Phe concentration for a 12-month period, only 32.1% of the samples attained the targeted Phe levels: for children < 13 years this was ≤ 360 μmol/L; for children ≥ 13 years, the target was ≤ 900 μmol/L [10].

Progressive deterioration in metabolic control has also been reported with age. Data from a survey of 10 European centers with a total of 1921 patients showed that at age one, the median blood Phe

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concentration was 175 μmol/L; between 1 and 3 years, the median was 230 μmol/L; between 4 and 10 years the median was 287 μmol/L; between 11 and 16 years the median was 465 μmol/L; and over 16 years the median was 777 μmol/L. Also, the median percentage of blood samples meeting guidelines tended to diminish with age [11].

Similar results were reported by Meli and Bianca [12]. In this sample, blood Phe concentrations were greater than the recommended value in none of the patients younger than 1 year of age, in 8% of the 1- to 6-year-olds, 18% of the 6- to 10-year-olds, 40% of the 10- to 14-year-olds, and 70% of those older than 14 years.

When trying to understand how compliance to treatment changes in different stages of life, what the underlying causes are, and the impact of non-compliance to treatment in PKU, it must be understood that there is no agreement regarding which compliance measures are most important and how they should be defined. As Mac Donald [8] proposes, direct assessment of blood Phe concentration is perhaps the best overall measure, but there is still no consensus regarding the number of Phe concentrations that should be within target range over time and the frequency or timing of the measure. Also, most studies of compliance in PKU focus on short periods (12 to 24 months) and follow the same patients over longer periods of time.

In Chile, the prevalence is 1/18,916 births for PKU and 1/10,198 births for mild hyperphenylalaninemia (mHPA). Since 1992, Chile has had a national neonatal screening program for phenylketonuria that covers 99% of newborns. Children with classical PKU (Phe ≥ 20 mg/dL [1200 μmol/L]), mild PKU (Phe 6 to 19 mg/dL [360 to 1190 μmol/L]) and also mHPA (Phe 2 to 6 mg/dL1[20 to 360 μmol/L]) enter a follow-up program for hyperphenylalaninemia (HPA) at the Institute of Nutrition and Food Technology (INTA), University of Chile national referral center. The follow-up program for children with PKU and mHPA includes regular measurements of Phe and tyrosine levels, as well as specialized assessments by a multidisciplinary team of pediatricians, nutritionists, neurologists, and psychologists. From diagnosis to adulthood multiple resources are used in patient education, from group workshops, written materials, individual/family education sessions, apps, among others.

Phe concentrations were both home monitored (samples taken at home and sent by mail) and monitored during clinical visits. Until 2010 the targeted blood Phe concentration of the Center was < 6 mg/dL during the first years of life and < 8 mg/dL (480 μmol/L) for patients age 10 years or older. Currently, the targeted blood Phe concentrations are ≤ 4 mg/dL (240 μmol/L) during the first year of life and < 6 mg/dL (360 μmol/L) after that. Nutritional treatment should be maintained for life. All PKU patients from birth to age 24 years have access through government subsidy to Phe free formula at no charge.

The present study seeks to describe and understand how treatment compliance changes through infancy, childhood, and early adolescence in PKU patients. We also aim to identify early indicators of poor treatment compliance and risk of treatment discontinuation that could be addressed to prevent poor cognitive outcome in early-diagnosed patients.

2. Subjects and methods

This longitudinal, retrospective study included all children diagnosed through newborn screening in Chile between February 2001 and October 2008 (age 7 years to 13 years 11 months, median age: 11.4 years). Data on a total of 75 patients (33 females and 42 males) with a mean age of diagnosis confirmation of 15.8 days of life (range 2 to 45; SD = 7.3) and average Phe blood concentration of 18.8 mg/dL (1138 μmol/L) (range 6 to 38.5 mg/dL; SD = 7.8) at diagnosis were analyzed. Treatment of all patients was initiated immediately after diagnostic confirmation. All included patients received a protein-restricted diet and had access to Phe-free formula at no cost, through government subsidy. No patients were receiving sapropterin treatment.

Yearly mean Phe concentration, number of blood samples sent, proportion of samples over the recommended range, and visits to the outpatient clinic were recorded for all patients. Given the relevance of early years on neurological development, data from the first year of life through age 4 years were analyzed separately in four groups, namely 0 to 11 months, 12 to 23 months, 24 to 35 months, and 36 to 48 months. Data from 4 years of age onward were analyzed in two-year periods, including 4 to 5 years and 11 months, 6 years to 7 years and 11 months, 8 years to 9 years and 11 months, 10 years to 11 years to 11 months, and 12 years to 12 years and 11 months.

Patients' treatment discontinuation was defined as no attendance to the outpatient clinic in a two-year period and no blood samples sent in a one-year period, both together.

Changes in the number of samples provided by the participants across the different assessment times were assessed with a repeated-measures ANOVA, Greenhouse-Geisser corrections were applied when sphericity assumptions were not met. Changes in blood Phe levels were assessed with a Friedman's ANOVA, since the variables were not normally distributed. Additional post hoc analyses were conducted using Wilcoxon signed-rank tests with a Bonferroni correction applied.

A hierarchical regression analysis was conducted to explore the prospective contribution of blood Phe levels measured across the participants´ first to seventh year of age to blood Phe levels at 8–10 years of age. Blood Phe levels measured at each assessment time were entered separately into the equation to control for the influence of earlier blood Phe levels. Results were tested against Bonferroni corrected p values.

The Shapiro-Wilk test was used to verify normal distribution of the data. Treatment adherence variables from individuals who did and did not discontinue treatment before 13 years of age were compared using Student's *t*-test. When normal distribution of a variable could not be proven, the nonparametric Mann-Whitney test was used. Additionally, child development and cognitive performance between groups was compared by using the nonparametric Mann-Whitney test. It was hypothesized that the participants in the group who discontinued treatment before 13 years of age would have poorer treatment compliance as expressed in all the measured variables. Therefore, significance was tested against 1-tailed p values.

A series of independent logistic regression analyses were conducted to ascertain the effect of the above mentioned treatment adherence variables measured at each assessment time on the likelihood that participants would discontinue treatment before 13 years of age. The variables were entered into the equation using the Enter method. Data were analyzed using SPSS 21.

3. Results

The results show a progressive increase in mean blood Phe concentrations with age. A Friedman's ANOVA analysis showed a statistically significant difference in blood Phe levels measured at different assessment times, $\chi^2(7) = 79.32$, $p = 0.000$. Post hoc analyses with Wilcoxon signed-rank tests were conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.007$. A significant increase in Phe levels was observed between the participant's first and second year of life ($Z = -3.869$, $p = 0.000$) with an increase of 1.1 mg/dL (66.1 μmol/L), and between the participants' second and third year of life ($Z = -2.756$, $p = 0.006$). There were no significant differences between blood Phe levels measured at 36–48 months and at 4 years–5 years 11 months of age. However, there was a statistically significant increase in blood Phe levels between the age ranges of 6–7 years 11 months of age and 8–9 years 11 months of age ($Z = -3.381$, $p = 0.001$).

By age ten, the mean Phe blood concentration of the group was above the recommended range (< 6 mg/dL) (Fig. 1).

As expected, the proportion of samples with Phe concentrations over 6 mg/dL (360 μmol/L) also increased with age, rising from an average of 13% during the first year of life to 67% in early adolescence.