U.PORTO

FACULDADE DE CIÊNCIAS DA NUTRIÇÃO E ALIMENTAÇÃO
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Transição entre cuidados pediátricos e seguimento especializado para adultos com fenilcetonúria (TRANS-PAC-PKU): impacto a 2 anos no controlo metabólico e na adesão ao tratamento

Transition from paediatric to adult care in phenylketonuria (TRANS-PAC-PKU): the 2 year's impact on metabolic control and adherence

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Trabalho de Investigação

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Resumo

Introdução: A transferência para cuidados de adultos (TAC) na PKU é desafiante e existe pouca evidência sobre seguimento de adultos. Pretendeu-se estudar o impacto da TAC no controlo metabólico e adesão à terapêutica.

Metodologia: Analisaram-se 55 doentes PKU transferidos entre 2011 e 2015 (55% mulheres; 5 HPA, 26 PKU moderadas, 24 PKU clássicas; 23.3±4.3 anos na TAC) nos períodos de estudo SP1 e SP2: 2 anos pré- e pós-TAC. Recolheram-se dados retrospetivos do controlo metabólico (mediana da [Phe] sanguínea, número de controlos, % de [Phe] < 8 mg/dL) e número de consultas em cada SP. Compararam-se as ingestões de proteína natural, equivalente proteico, proteína total (NP, PE, TP; g/kg) e Phe (mg/dia) na TAC e após SP2.

Resultados: Três doentes foram perdidos em follow-up no SP2. No SP1 vs. SP2, respetivamente: a mediana do número de controlos aumentou (22 [13-30] vs. 29 [15-41]; p=0.002); a média±DP da mediana da [Phe] sanguínea manteve-se (8.7±4.1 vs. 9.1±3.7; p=0.100); a mediana da % de valores < 8 mg/dL diminuiu (51.5 [3.7-95.7] vs. 36.5 [4.6-84.6]; p=0.041); a mediana de consultas aumentou (5 [4-6] vs. 11 [8-13]; p<0.001). A NP, PE, TP e Phe mantiveram-se: 0.46 [0.35-0.88] vs. 0.46 [0.28-0.94], p=0.873; 0.85 [0.47-1.10] vs. 0.83 [0.43-1.05], p=0.066; 1.51 [1.26-1.66] vs. 1.34 [1.07-1.54], p=0.194; 1210 [830-2311] vs. 1318 [763-2935], p=0.278.

Conclusão: A transição teve pouco impacto no controlo metabólico e houve poucas perdas em follow-up. A estabilização do padrão alimentar, aumento do número de consultas e manutenção dos mesmos nutricionistas pós-TAC terão contribuído para estes resultados.

Palavras-chave: Fenilcetonúria, Transição para cuidados de adultos, Controlo metabólico

Abstract

Background: In PKU, transfer to adult care (TAC) is challenging and information on adults follow-up is limited. We aimed to see how TAC affects metabolic control and adherence.

Methods: 55 PKU patients transferred between 2011 and 2015 (55% females; 5 HPA, 26 mild PKU, 24 classical PKU; 23.3±4.3 y at TAC) were analysed in the study periods SP1 and SP2: 2y pre- and post-TAC. Retrospective data on metabolic control (median blood [Phe], number of blood spots, % of blood [Phe] < 8mg/dL) and number of clinic visits was collected for each SP. Natural protein, protein equivalent, total protein (NP, PE, TP; g/kg) and Phe (mg/day) intakes closest to TAC and after SP2 were compared.

Results: Three patients were lost to follow-up in SP2. Findings in SP1 vs. SP2 were as follows: median number of blood spots increased (22 [13-30] vs. 29 [15-41]; p=0.002); mean±SD of median blood [Phe] remained stable (8.7±4.1 vs. 9.1±3.7; p=0.100); median % of blood [Phe] < 8 mg/dL decreased (51.5 [3.7-95.7] vs. 36.5 [4.6-84.6]; p=0.041); median number of clinic visits increased (5 [4-6] vs. 11 [8-13]; p<0.001). NP, PE, TP and Phe remained similar: 0.46 [0.35-0.88] vs. 0.46 [0.28-0.94], p=0.873; 0.85 [0.47-1.10] vs. 0.83 [0.43-1.05], p=0.066; 1.51 [1.26-1.66] vs. 1.34 [1.07-1.54], p=0.194; 1210 [830-2311] vs. 1318 [763-2935], p=0.278, respectively.

Conclusion: TAC had limited impact on metabolic control and few patients were lost to follow-up. Stabilization of dietary patterns, increase of clinical visits and inclusion of the same nutritionists after transition may have contributed to our results.

Keywords: Phenylketonuria, Transition to adult care, Metabolic control

List of abbreviations

HPA - Hyperphenylalaninemia

IMD - Inherited metabolic disorder

LT - Loading test

NBS - Newborn screening

NP - Natural protein

PAH - Phenylalanine hydroxylase

PE - Protein equivalent

Phe - Phenylalanine

PKU - Phenylketonuria

PS - Protein substitute

SP - Study period

TAC - Transfer to adult care

TNSPKU - Trends in nutritional status of patients with phenylketonuria

TP - Total protein

Index

Introduction

Phenylketonuria (PKU) is a rare autosomal recessive inherited metabolic disorder (IMD), most frequently caused by a mutation in the gene encoding phenylalanine hydroxylase (PAH). This enzyme hydroxylates phenylalanine (Phe) into tyrosine, so in PKU there is an accumulation of Phe in the blood and brain, with serious and irreversible neurotoxic effects [1].

PKU can be diagnosed through newborn screening (NBS), after which a lifelong treatment should be implemented as early as possible. The treatment is based on a low-Phe diet and its main goal is to keep blood [Phe] at acceptable levels, allowing for a normal neurocognitive outcome [2]. The PKU diet involves severe natural protein (NP) restriction, combined with the administration of a Phe-free protein substitute (PS) [1, 3].

Adherence to treatment is challenging and becomes increasingly difficult as patients reach adolescence and transition into adulthood [4]. Some of the main obstacles to dietary compliance include poor palatability of PS [5], difficulties with food preparation and restrictions on social life [6]. Accordingly, studies have shown that metabolic control usually deteriorates with age [7-11]. Moreover, many adults fail to attend clinic appointments, thus becoming lost to follow-up [7, 11, 12].

Despite recommendations of treatment for life, an international survey showed that only half of the included centres used standard treatment protocols or follow-up procedures for adults with PKU [13]. Also, many adult patients are still followed up by paediatric teams [11]. Given the specific comorbidity that is expected to occur in PKU adulthood [5, 14], the establishment of specialized adult care is recommended.

According to the new European guidelines for PKU, the transition from paediatric to adult care should be led as a structured process starting in early adolescence, at around the age of 12 years. During this process, management practices should become more directed at the patient instead of the caregiver. Then, the actual transfer to an adult treatment centre usually happens between 16 and 18 years of age [2].

Studies on the impact of transition in PKU are rare. However, it has been demonstrated in one centre that a successful transition and continuous follow-up for adults are achievable in most patients [15, 16].

Objectives

The aim of this single-centre study was to understand the effect of the transition from paediatric to adult care in terms of the quality of metabolic control and treatment adherence in patients with PKU.

Methods

Participants

All PKU patients transferred from paediatric to adult care at Centro Hospitalar do Porto between November 2011 and August 2015 were identified (n = 67). The date of transfer was defined by the first medical appointment with an adult physician.

A total of 12 patients were excluded: 10 were late diagnosed and had inconsistent dietary compliance, while 2 initiated sapropterin treatment during the study period, with possible influence on metabolic control.

A final sample of 55 patients (54.5% females) was studied. The disease severity was classified as described in the Portuguese consensus [17], according to the blood [Phe] at NBS: 5 patients (9.1%) had hyperphenylalaninemia (HPA, blood [Phe] < 6 mg/dL), 26 (47.3%) had mild PKU (blood [Phe] ≥ 6 and ≤ 20 mg/dL) and 24 (43.6%) had classical PKU (blood [Phe] > 20 mg/dL). Patients' age (mean ± SD) at transfer to adult care (TAC) was 23.3 ± 4.3 years (range 18 – 33 years).

Study design

This was an observational, retrospective and longitudinal study. All data was gathered from patient clinical records. Retrospective data regarding metabolic control and frequency of clinic visits was collected and analysed in two different study periods (SP): 2 years pre- and post-TAC (SP1 and SP2, respectively).

Weight and protein intake at TAC and after SP2 were also evaluated at two routine nutrition appointments, respectively intake 1 and 2 (**Figure I**). The first appointment considered was either on the day of TAC or, if no nutrition appointments were scheduled that day, the last one before transfer was used (n = 7). Intake 2 was recorded from the first appointment after SP2, which happened, in median, a month after this period (range 0 – 32 months).

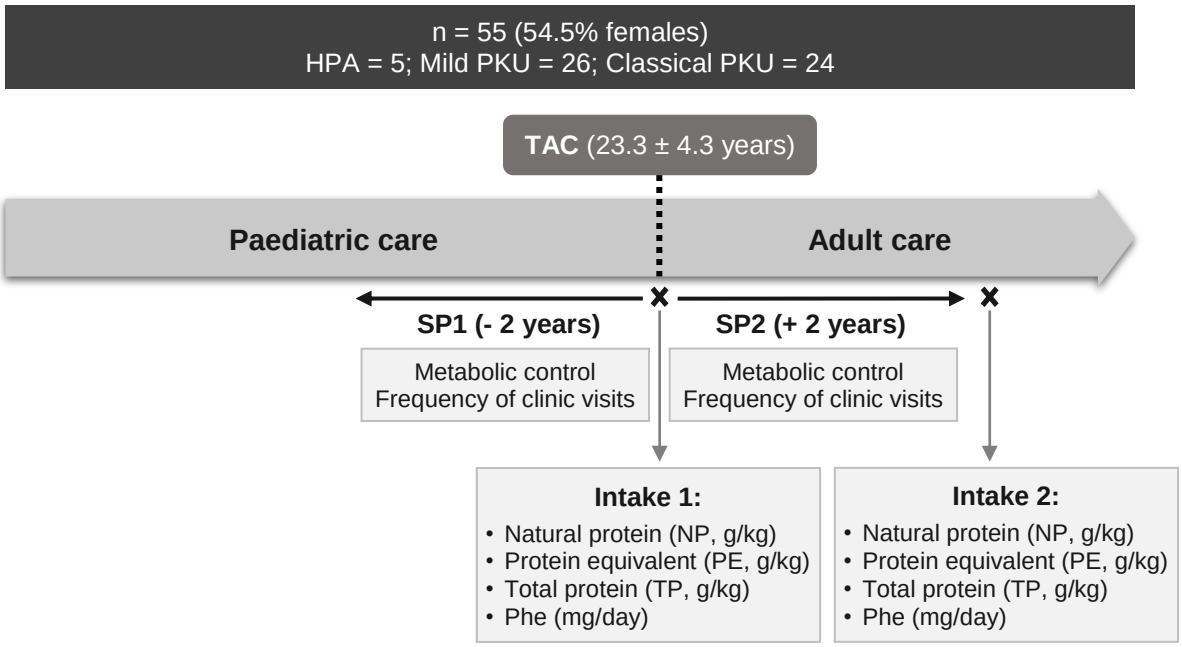

Figure I. Study design. *HPA*, hyperphenylalaninemia; *PKU*, phenylketonuria; *TAC*, transfer to adult care; *SP1*, study period 1; *SP2*, study period 2; *NP*, natural protein; *PE*, protein equivalent; *TP*, total protein; *Phe*, dietary phenylalanine.

Data collection

Metabolic control

Blood Phe concentrations were measured from dried blood spots collected at fasting state using tandem mass spectrometry. The number of analysed blood spots was registered and median blood [Phe] and % of measurements within the therapeutic range (< 8 mg/dL [17]) were calculated for each patient in SP1 and SP2. Patients enrolled to a BH_4 loading test (LT) in SP1 or SP2 were identified, considering this may have affected metabolic control.

Frequency of clinic visits

The number of attended, as well as missed, nutrition and medical appointments in each SP was determined after analysing electronic patient's clinical records.

Weight

Body weight was measured in light-weight clothes only, without shoes or adornments, using a Seca® mechanic scale with a precision of 0.5 kg.

Protein intake

Protein intake was recorded based on diet history questionnaires. The following intakes were calculated: natural protein (NP, g/kg/day), protein equivalent from PS (PE, g/kg/day), total protein (TP, g/kg/day) and Phe intake (mg/day).

Ethical statement

All the data collected in this study was under the ethical approval consented by the Ethics Committee of Centro Hospitalar do Porto, EPE, on 18th May 2015, to the investigation project TNSPKU (Trends in nutritional status of patients with phenylketonuria), with the reference 2015.101 (092-DEFI/087-CES). Every patient gave written informed consent.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 25 for Windows. The Kolmogorov-Smirnov test was performed to verify the normal distribution of variables. Categorical variables were presented as absolute values or percentages, while continuous variables were presented as means ± SDs or as medians [P_{25} – P_{75}]. Paired t-test and Wilcoxon test were used to identify differences between variables with normal and non-normal distribution, respectively. Statistical significance was considered when $p < 0.05$.

Results

Table I contains information regarding sex, disease severity, age at TAC, year of TAC and enrolment to a BH_4 LT. Despite including patients who were transferred to adult care in the course of five years, more than half of the patients (n = 31) were transferred in 2013 alone. It is also relevant to point out that a BH_4 LT was performed in nearly half of the patients included in the study (n = 24), all of which were done in SP2.

Table I. Sex, disease severity, age at TAC, year of TAC and submission to a BH_4 LT.

n = 55		
Sex [n (%)]	Female	30 (54.5)
	Male	25 (45.5)
Disease severity [n (%)]	HPA	5 (9.1)
	Mild PKU	26 (47.3)
	Classical PKU	24 (43.6)
Age at TAC (years)	Mean ± SD	23.3 ± 4.3
	Range	18 – 33
Year of TAC [n (%)]	2011	1 (1.8)
	2012	9 (16.4)
	2013	31 (56.4)
	2014	11 (20.0)
	2015	3 (5.5)
BH_4 LT [n (%)]	Yes	24 (46.2)
	No	28 (53.8)

Three patients (6%; 2 mild PKU females and 1 classical PKU male) failed to attend any appointments in SP2 and were therefore considered lost to follow-up, resulting

in a final sample of 52 patients. There was one unplanned pregnancy in SP2, however it was not completed due to a miscarriage.

The changes in metabolic control during the study are presented in **Table II** and illustrated in **Figure II**. The median number of analysed blood spots significantly increased from SP1 to SP2 (22 [13 - 30] vs. 29 [15 - 41]; p = 0.002), while the mean ± SD of the blood [Phe] median remained stable (8.7 ± 4.1 mg/dL vs. 9.1 ± 3.7 mg/dL; p = 0.100). The percentage of blood Phe measurements within the therapeutic range (< 8 mg/dL) significantly decreased in SP2 (51.5 [3.7 - 95.7] vs. 36.5 [4.6 - 84.6]; p = 0.041).

After stratifying the sample and analysing only the subjects who weren't submitted to a BH_4 LT, the increase in the number of blood spots lost statistical significance (22 [15 – 33] vs. 26 [12 – 37]; p = 0.374). In contrast, median blood [Phe] significantly increased in this subset of patients (6.2 [3.9 – 11.1] mg/dL vs. 6.8 [5.3 – 12.0] mg/dL; p = 0.001). Moreover, the percentage of blood [Phe] measurements within the therapeutic range still decreased in SP2, maintaining statistical significance (91.1 [15.7 – 100.0] % vs. 76.6 [11.9 – 96.7] %; p = 0.012).

Table II. Metabolic control of patients (n = 52) during the study period.

n = 52	**SP1**	**SP2**	**p**
Number of blood spots (n)	22 [13-30]	29 [15-41]	0.002
Median blood [Phe] (mg/dL)	8.7 ± 4.1	9.1 ± 3.7	0.100
[Phe] measurements < 8 mg/dL (%)	51.5 [3.7-95.7]	36.5 [4.6-84.6]	0.041

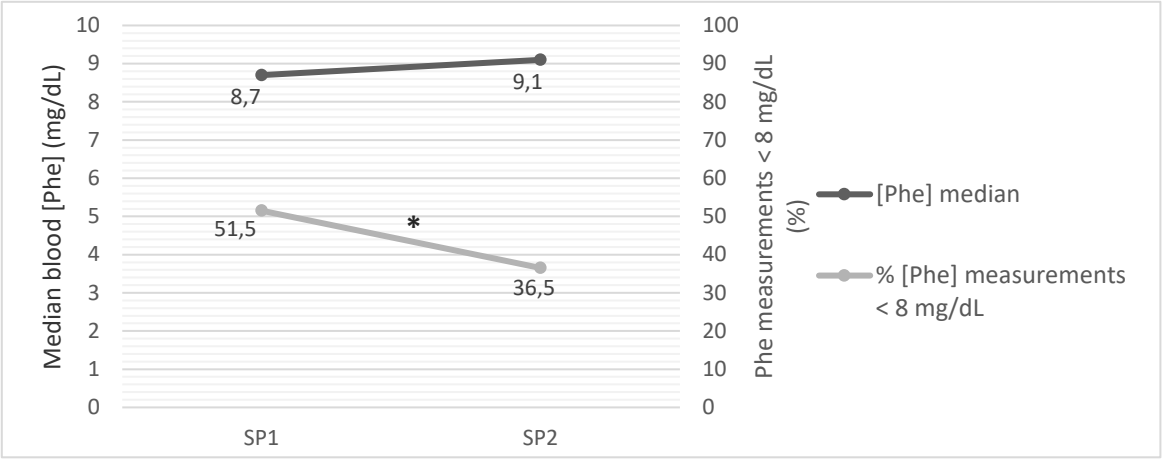

Figure II. Changes in metabolic control throughout the study (n = 52). *p = 0.041

As demonstrated in **Table III**, frequency of clinic visits increased to more than double after TAC. The increase in the median number of total appointments was the result of a higher frequency of nutrition, but mostly, medical appointments in SP2. In fact, 72.7% of patients didn't have any scheduled appointments with a physician in SP1 (data not shown), hence the median of zero appointments in this time period. A slight increase was also seen in the number of total missed appointments, with median attendance going from 100% in SP1 to 91% in SP2 (data not shown).

Table IV shows that protein and Phe intake remained similar between intake 1 and 2. There was a slight decrease in TP intake, while Phe daily intake increased, but these differences did not reach statistical significance.

Table III. Frequency of clinic visits in SP1 and SP2 (n = 52).

n = 52		**SP1**	**SP2**	**p**
Attended appointments (n)	Nutrition	5 [3-6]	7 [5-8]	<0,001
	Medical	0 [0-1]	4 [3-5]	<0,001
	Total	5 [4-6]	11 [8-13]	<0,001
Missed appointments (n)	Nutrition	0 [0-1]	0 [0-1]	0,014
	Medical	0 [0-0]	0 [0-1]	0,001
	Total	0 [0-1]	1 [0-2]	<0,001

Table IV. Daily protein and Phe intake (n = 52).

n = 52	Intake 1	Intake 2	p
Natural protein (NP) (g/kg/day)	0,46 [0,35-0,88]	0,46 [0,28-0,94]	0,873
Protein equivalent (PE) (g/kg/day)	0,85 [0,47-1,10]	0,83 [0,43-1,05]	0,066
Total protein (TP) (g/kg/day)	1,51 [1,26-1,66]	1,34 [1,07-1,54]	0,194
Phe (mg/day)	1210 [830-2311]	1318 [763-2935]	0,278

Discussion

The most important findings in this study were the fact that few patients were lost to follow-up after being transferred to adult care, and that the impact on metabolic control was limited.

The vast majority of patients (94%) still kept contact with the clinic two years after TAC. In one German centre, contact was maintained with only 81% of patients over a 3-year period [15]. A tendency for a higher loss of contact with male patients has also been reported [11], however that wasn't the case in this study.

The global median number of returned blood spots was significantly higher in SP2, and the same was found in the patients submitted to a BH_4 LT (data not shown). This was possibly due to the fact that blood [Phe] must be closely monitored prior to and during the test itself, in order to determine BH_4 responsiveness [18]. However, even in the group that was not submitted to a LT, the absolute number of blood spots showed a tendency to increase, although not reaching statistical significance. These results are still surprising, considering that the frequency of blood sampling usually deteriorates with increasing age [7, 9].

Another important finding was that even though the percentage of Phe measurements below 8 mg/dL decreased in SP2, this wasn't enough to significantly impact the overall blood [Phe] median. Together with an increased rate in the return of blood samples and the stability in protein intake, this seems to suggest that patients managed to preserve the quality of their metabolic control upon transition. Previous studies have found that adherence to blood [Phe] recommended ranges tends to decrease with age [7, 9, 10, 19, 20], whereas another study actually showed improved mean blood [Phe] after transfer from paediatric to specialized adult care [16].

During the 2 years pre and post-TAC, blood Phe levels remained slightly above the upper limit set by the Portuguese consensus for the treatment of PKU (8 mg/dL [17]). However, these results would be classified as within the target range defined in the new European guidelines, where the upper limit is 10 mg/dL [2].

In total, patients had more appointments after TAC, with little impact on overall attendance. The frequency of outpatient visits in both SP's exceeded the minimum requirement of two or one per year (for ages 12 – 18 years or ≥ 18 years, respectively) [2].

The increased frequency of nutrition appointments is probably related with sapropterin approval in Portugal, in 2014. With this, patients with mild and classical PKU from our centre were gradually enrolled to start Phe and protein titration in order to be prepared to a BH_4 LT. This may have led to an increased number of nutrition appointments. As previously described [21], NP intake was gradually increased until blood Phe levels above 8 mg/dL were achieved prior the test, which in turn required more frequent appointments with a nutritionist in order to perform dietary adjustments.

The absence of SP1 medical appointments in most patients can be explained by the model of transition implemented at Centro Hospitalar do Porto. All patients with IMD in our centre were used to be followed up by a team of metabolic paediatricians, nutritionists, a psychologist and geneticists, until reaching adulthood. Then, follow-up was continued although patients usually sought medical care outside the metabolic centre, as they were no longer able to attend a paediatrician. A protocol for the transition of metabolic patients to adult care was first established in 2009, when a team of adult physicians trained in IMD was assembled. From then on, patients aged 18 years or older were gradually transferred to an adult physician, while all the other healthcare professionals remained the same within the metabolic team. Diseases with a higher risk of metabolic decompensation, such as urea cycle disorders, organic acidurias, maple syrup urine disease and glycogen or fatty acid oxidation disorders were prioritized over others, such as PKU.

The transition in PKU only started in 2011 for adult patients of all ages, so naturally there was a wide age range at TAC (18 – 33 years). Most patients were already young adults, and mean age (23 years) was much higher than the recommended (16 – 18 years old) [2]. We could hypothesize that a higher age somehow contributed to the preservation of metabolic control in this 4-year period. This is because as patients grow older, they may start to perceive their condition as stable, and this might influence their adherence to treatment [22].

One of the main obstacles to a successful transition, as perceived by teenagers and their parents, is the anxiety towards having to leave their paediatric care provider of many years and changing to a new specialist [23]. In our centre, keeping the same experienced healthcare professionals throughout the transition, besides the

paediatrician, may help ease patients' concerns and increase their satisfaction regarding this process, as they already feel comfortable with the clinic staff.

This study had several limitations. Some confounding factors make the impact of TAC less clear, as they may have influenced metabolic control and adherence. For instance, the fact that many patients were exposed to an increased NP intake and that half of the sample endured a BH_4 LT, as already mentioned. Protein intake was estimated only on two different moments instead of throughout the whole study. Besides, because this was a retrospective study, the period of time in between those two moments was different for every patient. Moreover, not all contacts between patients and health professionals were accounted for in data collection (e.g. via phone, email), as these weren't registered in clinical records. There was also no data on how many adult patients attended local medical care in SP1.

Conclusion

The model of transition that was adopted in our centre seems to allow for a smooth transition of PKU patients from paediatric to adult care. The maintenance of most healthcare professionals throughout this process probably contributed to these results, however high mean age at TAC and exposure to a BH_4 LT make it harder to draw firm conclusions. Prospective multicentre studies would be useful to have a better understanding of the real impact of transition in patients with PKU.

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