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Poor adherence during adolescence is a risk factor for becoming lost-to-follow-up in patients with phenylketonuria

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ABSTRACT

Purpose: A high rate of lost to follow-up (LTFU) in patients with phenylketonuria (PKU) represents a main challenge. In this study, we investigated potential risk factors for becoming LTFU related to adolescence as a critical period of life.

Methods: We retrospectively analyzed longitudinal data collected from 1993 to 2019 of patients diagnosed with classic PKU that were followed at our center during adolescence (14–18 y) and at least once in adulthood (>18 y). Patients who interrupted their contact with our center after the 18th birthday for at least 2 years were classified as LTFU. We performed a multivariate regression analysis to investigate following potential risk factors for becoming LTFU in adult life: sex, dietary compliance during adolescence assessed through the mean of the annual medians of phenylalanine plasma values, average number of contacts with the center during adolescence and age at first visit after the 18th birthday.

Results: 93 patients (52 males, 41 females) were included in the study. 58% became LTFU during adulthood. The mean age at the last visit before becoming LTFU was 26.2 ± 5.1 years. In the multivariate Cox regression analysis we found that poor dietary compliance during adolescence was significantly associated with a higher risk of becoming LTFU during adulthood (p-value = 0.028).

Discussion: Adult patients who displayed poor treatment adherence during adolescence should be identified and carefully monitored to prevent loss of contact.

1. Introduction

Phenylketonuria (PKU, OMIM no. 261600) is an inherited autosomal recessive disorder caused by a loss of function of the enzyme phenylalanine hydroxylase leading to increased plasma phenylalanine (Phe) concentrations. With a global prevalence of 1:23,930 live births, PKU represents the most common inborn error of metabolism [1]. If untreated, PKU can lead to severe consequences in children such as intellectual impairment, growth failure, microcephaly, and seizures [2]. The detrimental effects of high Phe levels during adulthood are more subtle but still present, the main manifestations being impaired attention, inhibitory control and cognitive flexibility; depressed mood; anxiety; tremor; visual and motor disturbances [3,4]. These abnormalities can be prevented through a Phe-restricted diet, which represents the cornerstone of PKU treatment. Phe-restricted diet should be initiated right after diagnosis in the newborn screening and, according to current American and European guidelines [5,6], should be maintained for the entire lifetime in patients with untreated Phe levels >360 μmol/l [5] or > 600 μmol/l [6].

A main challenge in the management of adults with PKU is the high

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rate of patients who become lost to follow-up (LTFU), which is estimated to be between 33% and 77% [7–9]. LTFU patients presumably do not adhere to the Phe-restricted diet and may suffer from the consequences of high Phe levels. Up until now, information about the reasons beyond poor compliance and loss of contact with the clinic is mainly limited to surveys of PKU patients and PKU experts [10–12]. These real-life data are useful, however studies are needed to identify patients at risk for becoming LTFU in order to develop patient-specific strategies and ensure optimal care.

For patients affected by inherited metabolic diseases, adolescence represents a critical period characterized by multiple physical, psychological, and social challenges that impact treatment adherence [13]. Due to the importance of this critical period of life, our aim was to investigate potential risk factors for becoming LTFU related to adolescence of PKU patients. In particular, we explored the role of dietary compliance during adolescence (14–18 y), of the average number of yearly contacts with the clinic during adolescence and of the age at first visit after the 18th birthday. Furthermore, based on findings of our previous study suggesting that male patients may have a higher risk of becoming LTFU [9], we explored the role of sex. Year of birth was also included in the analysis as possible cofounding factor, since patients of older generations are known to have poorer adherence and higher rates of loss of contact [7,8].

2. Subjects and methods

2.1. Study design

We retrospectively analyzed longitudinal data of patients diagnosed with classic PKU in the Austrian newborn screening program between 1979-01-01 and 1999-12-31. We assessed data of PKU patients starting at age 14. Because the medical team of the Outpatient Metabolic Clinic began to actively reach out to LTFU patients to reestablish care in 2019, we defined 2018-12-31 as the end of the study.

Inclusion and exclusion criteria. Patients with classic PKU born between 1979-01-01 and 1999-12-31 were identified through the database of the Austrian newborn screening program. We included patients who were followed at our center as adolescents and at least once after their 18th birthday. Since preparation for pregnancy and pregnancy itself are bound to a more strict Phe control in women with PKU, we excluded female patients who became pregnant during the study observational period if the information about the beginning of their pregnancy or of the desire to have a child was missing.

Outcome parameters. We collected data regarding age, sex, blood Phe concentrations and number of contacts per year from age 14, and records of desire to have children or of pregnancy including date of first notification. To estimate the dietary compliance during adolescence, we calculated the mean of the annual median Phe values (Index of Dietary Control, IDC) [14] in the years 14–18. Furthermore, we calculated the mean number of contacts per year during adolescence. Patients who had no records of contact with our center for >2 years after their 18th birthday were classified as LTFU. For patients who became LTFU in our center in Vienna, staff members of the pediatric metabolic center in Salzburg checked whether they had contact with them in the two years after the last visit in Vienna due to change of residence. Data from the other two main metabolic Austrian centers placed in Graz and Innsbruck were not available.

Of note, the transition process at our clinic during the data collection period was not standardized, therefore it could not be taken into account in this study.

2.2. Statistical analysis

For the descriptive representation of the study population, mean and standard deviation were calculated for metric variables (age) and absolute and relative frequencies for categorical variables (sex, state of care). Survival analysis methods were used to answer the primary research question. The loss of contact as defined above counted as an event. Patients who visited the outpatient clinic in 2017 or 2018 for the last time during the observational study period were censored at the end of the study. Female subjects were also censored at the time where they notified their pregnancy or desire to have a child. In case of a known transfer to the metabolic center in Salzburg in the two years after the last visit in Vienna, patients were censored at the time of the last contact.

Multivariate Cox regression analysis was used to examine the influence of the above-mentioned risk factors on the probability of becoming LTFU to create a prognostic model. In particular, multivariate Cox Model was fitted in an exploratory fashion by first considering univariate models and then selecting among those predictors that were significant in the univariate analysis. Kaplan-Meier curves were created to illustrate the influence of the significant risk factors on contact interruption.

As secondary research question, we analyzed epidemiological characteristics and parameters of dietary compliance of the subgroup of patients who were followed at our clinic as adolescents but not as adults, and who were therefore excluded from the primary analysis.

Implementation of the database and data analysis were done using IBM SPSS Statistics, version 27 and R version 4.2.2.

This study was approved by the ethics committees of the Medical Universities of Vienna, and Salzburg (ethic approval numbers 1182/2021 and 1171/2021 and respectively).

3. Results

In the period between 1979 and 01-01 and 2018-12-31, 152 patients were diagnosed with classic PKU within the National Austrian Newborn Screening Program. After applying the inclusion and exclusion criteria, a total of $N = 93$ PKU patients (41 women, 52 men) were eligible for the final data set (Fig. 1).

Table 1 summarizes the epidemiological characteristics of the study cohort as well as the descriptive statistics of IDC during adolescence, average number of yearly contacts during adolescence and age at first visit as adults. 54 patients (58.0%) became LTFU in adulthood during

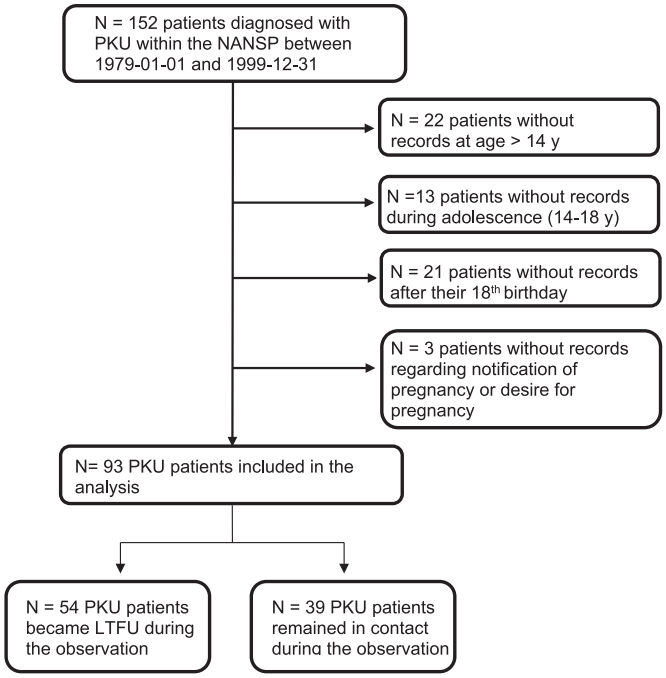

Fig. 1. Flowchart selection of study population. Abbreviations: PKU, Phenylketonuria; NANSP, national Austrian newborn screening program; LTFU, lost to follow-up.

Table 1
Epidemiological characteristics of the study cohort ($n = 93$).

Sex	
Women, n (% of study cohort)	41 (44.0%)
Men, n (% of study cohort)	52 (56.0%)
Lost to follow-up	
n (% of study cohort)	54 (58.0%)
Age at last visit before losing contact	
Mean ± standard deviation (y)	26.2 ± 5.1
Patients with a pregnancy during the observation	
n (% of study women)	6/42 (14.2%)
Age at pregnancy	
Mean ± standard deviation (y)	25.7 ± 2.3
Index of dietary control during the years 14–18 y	
Mean ± standard deviation (mg/dL)	13.1 ± 5.9
Q1; Q2; Q3 (mg/dL)	8.7; 12.9; 17.1
Average number of contacts during the years 14–18 y	
Mean ± standard deviation (contacts/y)	5.8 ± 3.4
Q1; Q2; Q3 (contacts/y)	3.0; 5.3; 7.8
Age at first visit after 18th y	
Mean ± standard deviation (y)	18.9 ± 2.3
Q1; Q2; Q3 (y)	18.1; 18.2; 18.5
Censoring	
n (% of study cohort)	7 (7.5%)
Reasons for censoring	
- Pregnancy, n	4
- Change of clinic, n	3

Abbreviations: Q, quartile.

the observational study period. The mean age ± SD at the time of contact loss was 26.2 ± 5.1 years. Six of the 41 women (14.2%) in our cohort were pregnant at some point during the observational period with a known date of pregnancy onset or desire to become pregnant. Of the six women, four were censored at the time of notification of desire for pregnancy, whereas two had a loss of contact with the clinic longer than two years before pregnancy and were therefore classified as LTFU. Three patients were censored due to change of clinic.

In the initial univariate Cox regression analysis (Table 2), a significant association with loss of contact was observed for all variables except for sex.

In the multivariate Cox regression (Table 3), the IDC during adolescence remained highly significantly associated with the risk of losing contact with the clinic (p-value = 0.028). Specifically, higher IDC indicating poorer compliance correlated with an increased risk for loss of contact. As expected, patients of the older generation showed a trend towards an increased risk of becoming LTFU compared to the younger generation.

Fig. 2 illustrates the Kaplan-Meyer plot for IDC where the loss of contact with the clinic represented the registered event.

The subgroup exploratory analysis showed that 21 adolescent patients interrupted their care before reaching the 18th year of age (four females, 17 males; current age, mean ± SD: 37 ± 6.4 y; average number of yearly contacts during adolescence, mean ± SD: 2.0 ± 1.7 contacts/y; IDC during adolescence, mean ± SD: 19 ± 6.5 mg/dl). Compared to the patients who became LTFU as adults, the patients who were lost in transition had comparable age (two-tailed unpaired t-test, $p = 0.09$), significantly higher IDC and fewer contacts with the clinic during adolescence (two-tailed unpaired t-test, $p < 0.001$ for both parameters). Male sex was more frequent in the lost in transition group than in the study cohort (80.9% vs. 55.0%).

Table 2
Univariate Cox regression analysis for the independent variables sex, index of dietary control (IDC) and average number of contacts per year during adolescence (14–18 y), age at first visit as an adult (>18 y) and year of birth with the dependent variable loss of contact.

	coefficient	HR	Lower 95% CI	Upper 95% CI	p-value
Sex	−0.162	0.851	0.488	1.482	0.568
Index of dietary control during the years 14–18 y	0.082	1.086	1.041	1.133	0.000
Average number of contacts during the years 14–18 y	−0.093	0.911	0.836	0.993	0.034
Age at first visit after 18th y	0.145	1.156	1.073	1.246	0.000
Year of birth	−0.076	0.927	0.879	0.978	0.006

Table 3
Multivariate Cox regression analysis for the independent variables index of dietary control (IDC) and average number of contacts per year during adolescence (14–18 y), age at first visit as an adult (>18 y) and year of birth with the dependent variable loss of contact.

	coefficient	HR	Lower 95% CI	Upper 95% CI	p-value
Index of dietary control during the years 14–18 y	0.051	1.053	1.006	1.102	0.028
Average number of contacts during the years 14–18 y	−0.048	0.953	0.872	1.041	0.284
Age at first visit after 18th y	0.063	1.065	0.956	1.186	0.254
Year of birth	−0.053	0.948	0.898	1.002	0.057

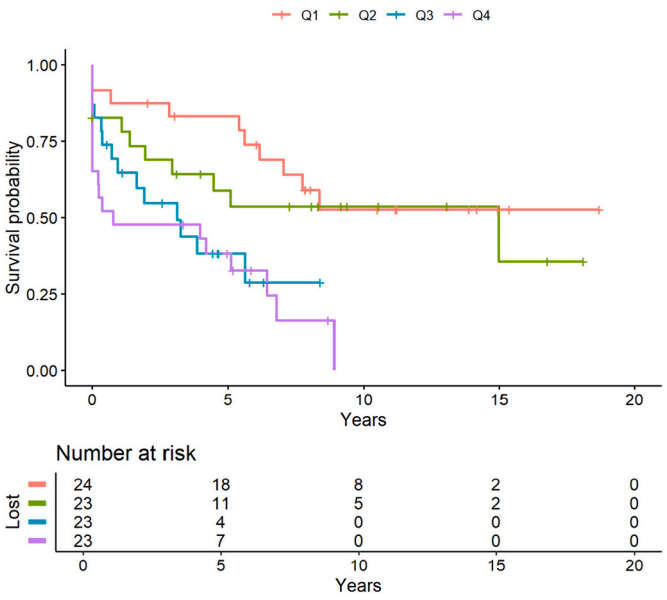

Fig. 2. Kaplan-Meier curves depicting the risk of loss of contact as a function of the Index of Dietary Control variable (mean of annual median phenylalanine levels between 14 and 18 years of age). Curves are shown for the different percentile groups (Q1-Q4).

4. Discussion

In this observational, longitudinal study with an historical cohort of 93 PKU patients, we found that higher IDC scores, representing poorer dietary adherence in adolescence, were significantly associated with a higher risk of becoming LTFU in adulthood. These findings show that the adherence during adolescence is critical for the future state of care.

According to the findings of cross-sectional studies, the rate of adult PKU patients who become LTFU lies between 33 and 77% [7–9]. These data are consistent with the results of our longitudinal study, in which 58% of PKU patients interrupted contact with our clinic. In our previous multicenter study of LTFU patients in Austria, we reported that the percentage of LTFU patients was 67.9% among men and 57.1% among

women [9]. The difference between the sexes did not reach statistical significance, however it suggested that male sex could represent a risk factor for becoming LTFU. In the current study, we found that sex was not significantly associated with the risk of becoming LTFU after all. A possible reason for this discrepancy is that patients of the current cohort are younger compared to that of Beghini et al. due to the different inclusion criteria (year of birth 1979–1999 versus 1966–1999 [9]). This leads to a selection bias because the first PKU guidelines recommended the low-Phe diet only during childhood. Moreover, we here observed that two women who were classified as LTFU came back spontaneously due to a pregnancy on a later time point. It is possible that in Beghini et al. women were underrepresented in the LTFU category due to pregnancy at the time of the observation [9].

To our knowledge, we are the first research group that conducted a longitudinal study with a relatively large PKU cohort to investigate possible adolescence-related risk factors for the loss of contact with the clinic as adults. Our findings point to the importance of assessing the IDC of adolescent PKU patients, which remained significant even when considering year of birth as a cofounding factor. Based on our data we recommend to assess dietary compliance during adolescence (e.g. in the form of IDC) when patients present at the adult clinic after the transition, so that this crucial information can be taken into account from the beginning in the new adult setting. Patients at higher risk of becoming LTFU should be monitored more carefully and receive intensive care including accurate dietary counseling and information about the consequences of uncontrolled PKU. The literature mentions numerous reasons why patients with PKU have difficulties with treatment adherence including restrictions of sociability due to the Phe-restricted diet, high treatment costs, poor knowledge of the effects of high Phe plasma levels, and unfamiliarity with guideline recommendations for lifelong continuation of PKU treatment [10,11]. These factors should be addressed accurately when approaching PKU patients during and after the transition. Some of these factors are specific to the country or health system, so it is not always possible to generalize recommendations. Based on our findings, we think that in young adult patients, especially if treatment adherence was suboptimal in adolescence, a more detailed social history and analysis of the patient setting for possible difficulties or obstacles in the implementation of the diet should be collected. On a positive note, the expanded choices now available in foods on the market, as well as the new options in therapies that allow at least a subgroup of patients for a more Phe-rich diet (e.g., Kuvan® or Palynziq®), are important factors that can effectively help achieve better adherence [12].

It is noteworthy that in our cohort patients lost contact on average at a rather young age, suggesting that the interventions should continue during in the first years of the adult care.

In this study, we only included patients who had been in our care as adolescents and at least once as adults. 21 patients who lost their contact during adolescence were therefore not considered in the primary analysis. We found that the patients who were lost at this early phase had significantly higher IDC and fewer yearly contacts with the clinic during adolescence compared to patients who became LTFU later in life. These data further support the role of IDC as useful tool to estimate the risk of losing contact with a patient. Remarkably, male sex was more frequent in the younger LTFU group than in the study cohort. This may explain the discrepancy we observed in the role of sex in our two studies [9]. Further studies should investigate this particular group to characterize it and develop strategies to improve care.

For our aim, we focused on compliance during adolescence as a critical period before the transition process. However, it is possible and even likely that patients who showed poor compliance during adolescence displayed higher Phe values well before 14 years of age as well. This research question is beyond the scope of the current study and should be subject of research in pediatric patient cohorts to clarify risk factors related to poor compliance at younger ages.

4.1. Strengths and limitations

One of the main strengths of the current study is the relatively large cohort of 93 patients. To our knowledge, we are the first to attempt to identify risk factors for loss of contact in PKU patients, although this problem has long been known and widely discussed. Considering the scarceness of information on the management of LTFU-PKU patients, our study provides relevant findings that can help in the clinical practice. Our study has some limitations that should be mentioned. Since this was an observational study conducted over a long period, there are a number of possible confounding factors that could not be accounted for (e.g., different follow-up policies, different transition standards, use of Kuvan®, sociodemographic factors). All data were obtained from our centers in Vienna and in Salzburg; therefore, we cannot exclude the possibility that some patients who were classified as LTFU continued to receive care at another center due to change of residence. Finally, due to the retrospective nature of the study, further relevant factors for treatment adherence in PKU could not be investigated.

Funding

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Implication and contribution summary statement

Higher plasma phenylalanine values during adolescence are a significant predictive parameter for loss of contact with PKU patients in early adulthood. Dietary compliance during adolescence should be assessed after the transition to identify patients at risk of becoming LTFU in order to implement appropriate preventive measures.

CRediT authorship contribution statement

Marianna Beghini: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Maximilian Pichler:** Writing – review & editing. **Fiona Carolina Tinnefeld:** Writing – review & editing, Conceptualization. **Matthäus Metz:** Writing – review & editing. **Dorothea Möslinger:** Writing – review & editing, Data curation. **Vassiliki Konstantopoulou:** Writing – review & editing, Data curation. **Johannes Spenger:** Writing – review & editing, Data curation. **Alexandra Kautzky-Willer:** Writing – review & editing. **Florian Frommlet:** Writing – review & editing, Formal analysis. **Thomas Scherer:** Writing – review & editing, Conceptualization. **Miriam Hufgard-Leitner:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

All authors declare no conflict of interest.

Data availability

Data will be made available on request.

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