Therapy compliance in children with phenylketonuria younger than 5 years: A cohort study

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Abstract

Background. Phenylketonuria (PKU) is a metabolic disease. It is manifested by a complete or partial inability to convert phenylalanine (Phe) to tyrosine and leads to increased concentrations of Phe in the blood and in other tissues, including the brain, causing irreversible neurological damage if left untreated. Low-phenylalanine diet is a key component of classical PKU therapy.

Objectives. The objective of this study was to assess the effectiveness of classical phenylketonuria therapy and compliance with doctors' recommendations in the first 5 years of life.

Material and methods. Data was collected from all diagnosed and treated patients (n = 57) born 1999–2010. Phenylalanine blood levels, the number of visits to a specialist outpatients' center, the number of blood tests, as well as socioeconomic status (SES) and parents' education level have been analyzed, and potential relationships have been assessed.

Results. In the 1st year of life patients visited their doctors (odds ratio (OR) = 6.8267; 95% confidence interval (95% CI) = 2.827–16.5163; p < 0.0001) and had their blood collected (OR = 2.7875; 95% CI = 1.0467–7.4234; p < 0.0402) significantly more frequently than in the 2nd year. This tendency persisted into subsequent years. Similarly, in infancy they had statistically significantly lower odds of exceeding more than 40% of their Phe levels over therapeutic range than 1 year later (OR = 3.6078; 95% CI = 1.4859–8.7599; p < 0.0046). No PKU child had more than 70% of Phe levels over the therapeutic range in the 1st year of life, whereas 4 years later there were 18 such children. Phe levels were correlated with the number of visits to a specialist (p = 0.39) and the number of Phe blood tests with index of dietary control (p = –0.33). The effectiveness of therapy and compliance with the doctor's recommendations seem to depend neither on the level of education of the patient's parents nor on their SES.

Conclusions. Therapy effectiveness and patients' compliance in PKU is very good in infancy. However, both deteriorate in subsequent years. Moreover, they do not seem to depend on the family background.

Key words: compliance, diet, phenylketonuria, inborn errors of metabolism, phenylalanine

Introduction

Phenylketonuria (PKU) is currently regarded as a model inborn error of metabolism, which, if the treatment is not started immediately after birth, leads to irreversible damage to the central nervous system. Metabolic pediatrics often uses the experience gained in treating that illness over the years, from extending screening of the newborn, through the strategies of medical care for diagnosed patients, to the control of the effectiveness of the therapy.¹ A constitutive element of the strategy of complex care of patients suffering from PKU is the creation of an effective system of medical and dietary supervision that allows the patients to function in society under the conditions as close as possible to those of their healthy peers. Research conducted over the years has shown certain deficits in treated patients with PKU. At the same time, however, we are confident that to achieve the best outcomes, PKU must be diagnosed early, and the low-phenylalanine (Phe) diet effectively implemented. The strategy of medical care for patients with PKU includes, among others, the monitoring of the serum Phe levels, effectively planned and carried out visits to a dietician, and medical and psychological examinations. Both for the parents of a PKU child and for the doctor, the results of blood tests are the first step in the evaluation of the effectiveness of the treatment, and they allow the doctor and parents to modify the child's diet in order to achieve the best therapeutic effect.

In 1956 Blainey and Gulliford drew attention to the diet non-compliance during the homestay of PKU children.² Because they were among the first specialists working with PKU patients, one can say that the problems with the diet compliance are almost as old as the treatment of the disease itself. On the other hand, despite the time that has since passed, it is still believed that "compliance assessment measures remain inadequately defined. The direct assessment of blood Phe concentration is perhaps the best overall measure, but there is no universal agreement about the number of Phe concentrations that should be within target range and frequency or timing of measurement."³

Objectives

The purpose of this article was twofold. Firstly, the effectiveness of PKU therapy in the first 5 years of life of a patient has been assessed on the basis of Phe levels in blood, the compliance with dietary recommendations based upon the number of visits to a specialist and the number of blood tests. In particular, we have analyzed how the values of these parameters change in time, and whether there is any internal correlation among them. Secondly, we attempted to verify a hypothesis about a link between these 3 parameters and the family background of a patient as expressed by the parental educational level and the socioeconomic status (SES) of the family.

Material and methods

A retrospective longitudinal study was conducted in a group of classical PKU patients, diagnosed from May 1999 to September 2010, who were admitted for diagnosis and treatment at the Department of Pediatric Gastroenterology and Metabolic Diseases at the Poznan University of Medical Sciences, a reference unit for PKU patients from western Poland. For the purposes of our analysis, patients with classical PKU were defined as those who require a low-phenylalanine diet to maintain plasma Phe levels within the target range of 2–6 mg% (120–360 $\mu\text{mol/L}$) and whose Phe levels without diet exceed 20 mg% (1200 $\mu\text{mol/L}$).^{4,5} The inclusion criteria were the following: neonatal diagnosis carried out with the colorimetric method, classical PKU diagnosed and continuous treatment for at least 5 years. The exclusion criterion was a chronic or acute disease which may influence PKU treatment. Our department is taking care of 57 PKU patients (37 girls and 20 boys) born between May 1999 and September 2010. All 57 patients participated in the study, with no one excluded from this group. There were 2 more PKU patients diagnosed in this period: a girl who died at the age of 2 of another disease, and a boy whose parents after 1 year of diet refused any further treatment for their son.

All records of each patient's visit to a specialist were collected from the clinical documentation for comparison with recommendations regarding the number of visits. The parents of a PKU child are informed that for the first 3 years of life the child should visit a specialist every 3 months. Later in life the control should be carried out every 6 months. The compliance percentages with these recommendations were calculated for each year of the child's life separately. We also collected information about the SES and educational level of the parents of all the patients.

We evaluated all the blood Phe concentrations collected during the first 5 years of the children's lives, with the exception made for the 1st month, because Phe concentrations in this period are unstable. For each patient, we counted the number of tests to compare it with the recommendations. The 5-year index of dietary control (IDC) was calculated as the mean of the 12-month medians. The percentage of Phe concentrations which were within the therapeutic range was analyzed for each patient and each year of life.

Since this was an exploratory study, sample size was not calculated and all the available data was gathered. The Shapiro–Wilk test was applied to determine the normality of the data distribution. Results are expressed as medians and interquartile ranges (IQRs; means $\pm$ SD). The odds ratio (OR) was calculated to compare the following: 1) the percentage of results beyond the therapeutic range taken from the data from the first 5 years of life, 2) the number of medical visits and Phe blood sampling (compared were the results for the years of life grouped into two groups: one group comprising the 1st, the 2nd and the 3rd year of life, and the other – the 4th and the 5th years, the assumption being that

recommendations for patients aged 1–3 years differ from those for 4–5 years of life). The 95% confidence intervals (95% CI) were calculated to estimate the precision of the OR.

Spearman's rank correlation coefficient was calculated to determine possible correlations between, on the one hand, the educational level of the mother, the educational level of the father, the SES of the family and the sex of the child, and on the other hand, the following parameters: the number of visits to a specialist and the frequency of Phe blood monitoring. Then, possible correlations between all the 6 abovementioned factors, and both IDC and the percentage of Phe concentrations within the therapeutic range were also tested with Spearman's coefficient.

The level of significance was set at $p < 0.05$. Statistical analysis was performed using STATISTICA v. 12 (StatSoft Inc., Tulsa, USA).

The study adhered to the Declaration of Helsinki and was approved by the Bioethical Committee at the Poznan University of Medical Sciences (approval No. 268/15).

Results

During the first 5 years of life, 57 PKU children visited a specialist 806 times and had their blood monitored for Phe 7,638 times. The mean number of visits to the specialist over the first 5 years of life was 14.1 (range: 6–29).

In the 1st year of life, the mean number of visits was 4.7, decreasing to 2.5 in the 3rd year and to 1.7 in the 5th year (Table 1). As the recommended number of visits was lower in year 4 and 5, the lowest mean percentage of the recommended number of visits was in the 3rd year – 62%.

The mean number of blood Phe monitoring in the 1st year was 44.4 (range: 7–73) (Table 2). In the 5th year, the mean number of blood Phe monitoring decreased to 15.3. In the 4th and 5th year, there were children with no blood Phe monitoring at all. The mean number of blood Phe monitoring during the first 5 years varied from 21 to 239, so from 10% to 115% of the recommended value, with the mean value of 137 (66%).

During the 1st year of life, 32 patients out of 57 (56%) had less than 20% of Phe blood test results over the therapeutic range of 6 mg% (Table 3). During the 5th year of life, there were only 15 (26%) such patients. We found no PKU child with more than 70% of Phe blood test results over the therapeutic range in the 1st year of life. In the 5th year of life, there were 18 such children. During the 1st year, the mean value of blood Phe concentrations was 3.6 mg%, and the median was 3.2 (Table 3). In the consecutive years, the mean value increased, reaching 7.1 mg% in the 5th year, and the median increased to 5.7 mg%. The maximum value was observed in the 4th year (5.9 mg%).

During the 1st year of life, patients had statistically significantly lower odds of exceeding Phe therapeutic range

Table 1. Number of visits to a specialist

Years of life		1 st	2 nd	3 rd	4 th	5 th	1 st –5 th
Number of visits to a specialist	range	2–9	0–8	0–7	0–5	0–4	6–29
	median (IQR)	5 (4–5)	3 (2–4)	2 (2–3)	2 (1–3)	2 (1–2)	14 (11–17)
	mean (SD)	4.7 (1.4)	3.3 (1.4)	2.5 (1.3)	1.9 (1.1)	1.7 (0.9)	14.1 (4.4)
Recommended number of visits		4	4	4	2	2	16
Number of visit as % of recommendations	range	50–225	0–200	0–175	0–250	0–200	37–150
	median (IQR)	125 (100–125)	75 (50–100)	50 (50–75)	100 (50–150)	100 (50–100)	87 (69–106)
	mean (SD)	117 (35)	82 (35)	62 (32)	95 (55)	85 (45)	88 (27)

IQR – interquartile range; SD – standard deviation.

Table 2. Number of Phe blood tests

Years of life		1 st	2 nd	3 rd	4 th	5 th	1 st –5 th
Number of blood Phe tests	range	7–73	3–58	1–52	0–48	0–46	21–239
	median (IQR)	47 (35–55)	34 (21–45)	25 (13–36)	15 (10–26)	13 (8–19)	137 (92–175)
	mean (SD)	44.4 (14.6)	32.5 (15.1)	24.7 (13.6)	18.1 (10.4)	15.3 (8.6)	134 (54)
Recommended number of blood tests		52	52	52	26	26	208
Number of blood tests as % of recommendations	range	13–140	6–111	2–100	0–185	0–177	10–115
	median (IQR)	90 (67–106)	65 (40–86)	48 (25–69)	58 (38–100)	50 (31–73)	66 (44–84)
	mean (SD)	85 (28)	62 (29)	47 (26)	70 (40)	59 (33)	64 (26)

IQR – interquartile range; SD – standard deviation.

Table 3. Phe blood levels over the therapeutic range and mean Phe blood concentrations

Abnormal results	Number of patients with Phe levels over the therapeutic range				
	Years of life				
	1 st	2 nd	3 rd	4 th	5 th
<20%	32	23	21	20	15
21–40%	16	11	11	9	14
41–70%	9	15	10	14	10
>70%	0	8	15	14	18
Mean blood Phe concentrations [mg%]					
Years of life	1 st	2 nd	3 rd	4 th	5 th
Range	1.4–7.7	2.6–13.2	1.3–24.7	2.6–24.7	2.1–24.8
Median (IQR)	3.2 (2.6–4.4)	4.5 (3.6–6.9)	5.1 (3.9–8.9)	5.9 (4.0–7.4)	5.7 (4.2–8.3)
Mean (SD)	3.6 (1.6)	5.5 (2.4)	6.5 (4.3)	6.6 (4.2)	7.1 (4.7)

IQR – interquartile range; SD – standard deviation.

Table 4. Comparison of Phe levels and parental compliance between particular years

Phe levels over therapeutic range (OR (95% CI))				
Percentage	Years of life			
	2 nd vs 1 st	3 rd vs 1 st	4 th vs 1 st	5 th vs 1 st
<20%	1.8922 (0.8991–3.9823) 0.0930	2.1943 (1.0359–4.6480) 0.0402	2.3680 (1.1133–5.0368) 0.0252	3.5840 (1.6295–7.8829) 0.0015
<40%	3.6078 (1.4859–8.7599) 0.0046	4.1667 (1.7222–10.0807) 0.0015	5.1494 (2.1333–12.4299) 0.0003	5.1494 (2.1333–12.4299) 0.0003
Parental compliance (OR (95% CI))				
Event	Years of life			
	2 nd vs 1 st	3 rd vs 1 st	3 rd vs 2 nd	5 th vs 4 th
Visits	6.8267 (2.8217–16.5163) <0.0001	20.0000 (7.6948–51.9831) <0.0001	2.9297 (1.2850–6.6795) 0.0106	1.0751 (0.5099–2.2669) 0.8491
Phe blood tests	2.7875 (1.0467–7.4234) 0.0402	10.7317 (2.3363–49.2947) 0.0023	3.8500 (0.7638–19.4057) 0.1024	3.7143 (1.2478–11.0558) 0.0184

OR – odds ratio; CI – confidence interval.

than later in life (Table 4). Statistically significant OR were found between the number of visits to a specialist and a number of blood Phe tests in the 1st vs 2nd and 3rd year of life. No relationship was found between, on the one hand, the parental educational level and the SES of the family, and on the other, the number of visits to the specialist and the frequency of Phe blood monitoring (Table 5).

Statistically significant correlations were found between, on the one hand, the percentage of Phe concentrations within the therapeutic range and IDC, and on the other, the number of visits to the specialist and the frequency of Phe blood monitoring (Table 5). No statistically significant correlations of the parental educational level and the SES of the family with the percentage of Phe concentrations within the therapeutic range and IDC were documented.

Discussion

In this unique study comprising all PKU patients treated in our department, we aimed to assess the effectiveness of therapy and compliance with specialists' recommendations in the first years of life. It is worth emphasizing that although treatment control of PKU patients in infancy was very good, still many parents did not strictly follow given dietary recommendations. In subsequent years, significant deterioration was observed, which points to the need of further parental education and intensification of medical care. Unexpectedly, we did not observe any impact of parental education or socioeconomic status.

In an analysis of rare diseases, including inborn errors of metabolism, a common obstacle in achieving reliable results of tests is the size of the study group and

Table 5. Correlations between Phe levels, family background and the number of visits and frequency of blood testing

Variable	% of measured Phe levels within therapeutic range		IDC		Number of visits		Number of blood tests	
	ρ	p	ρ	p	ρ	p	ρ	p
Educational level of mother	0.20	0.14	−0.04	0.77	0.08	0.55	0.11	0.41
Educational level of father	0.21	0.12	−0.11	0.40	−0.05	0.72	0.02	0.89
SES	0.18	0.19	−0.12	0.36	0.13	0.32	0.20	0.14
Number of visits to the specialist	0.39	0.003	−0.30	0.02	–	–	–	–
Number of blood tests	0.26	0.05	−0.33	0.01	–	–	–	–

Phe – phenylalanine; IDC – index of dietary control; SES – socioeconomic status.

its representativeness for the entire patient population. If the survey covers only a part of the patient population, the risk of bias increases. The present study is unique, because 100% of the treated PKU patients in our hospital were included in the study and the whole experimental group was enrolled on the basis of uniform criteria. This allowed for a reliable assessment of patient compliance (the number of visits and blood tests, and especially the concentration of Phe) in the largest PKU patients group to date.

The literature concerning the number of medical visits and practices associated with it during the treatment of PKU is not too extensive. There is no doubt that of crucial importance is the number and schedule of a PKU patient's visits to a specialist, because it is during those visits that knowledge about the disease is transmitted; these visits exert a disciplinary influence on the parents and contribute to the correction of their misconceptions drawn, e.g., from the Internet. Similarly to the recommendations on the number of blood tests, there are also recommendations on the minimal frequency of visits to a specialist. The PKU Consensus Development Conference Statement, released in 2000, suggests “regular and frequent visits to a PKU clinic”.⁶ The National Society for Phenylketonuria (UK) recommends as a minimum, until 2 years of life, a 3-monthly review, for patients aged less than 5 years – a 4-monthly review, and later – a 6-monthly review.⁷ German recommendations⁸ suggest at least 1 clinical monitoring per quarter until 4 years of age and every 3–6 months until 12 years of age. The analysis done by van Spronsen et al.,⁹ conducted in 17 European PKU centers in 12 countries, as a suggested frequency of clinical evaluation in the 1st year of life gives from 2 to 12 (with the most frequent value 9), and for the next 3 years of life from 1 to 6 visits per year (with the most frequent value being 4). In the recently published European guidelines for the diagnosis and management of patients with PKU,¹⁰ the researchers suggest a visit to a specialist every 2 months in the 1st year of life, and then twice per year until 12 years of age. In Poznań, parents are informed that for the first 3 years of life, children should visit a specialist

every 3 months. Later in life, control should be carried out every 6 months.

In the group that took part in the present study, the average number of visits to the specialist in the first 5 years of life was 14.1 (while the recommended number was 16). More than 50% of the patients did not comply with the recommendations. One-third of the visits (269 of 806) took place in the 1st year of life. A significant part of the analyzed group also had periods without medical examination, sometimes even exceeding 1 year. The analysis of the visits is hindered by random events, such as, e.g., infections, which can cause a temporary increase of Phe in the blood, and hence should lead to a visit to a specialist. Circumstances not directly related to the disease (such as the need to obtain a certificate for the purposes of the foundation supporting PKU children) could also have had an impact on the number of visits. Despite all the factors that influenced the number of visits in this study, we observed a significant correlation between the number of visits and the number of blood tests ($\rho = 0.44$ at $p = 0.0006$). The analysis of our data disaggregated by years revealed a correlation only in the 3rd, 4th and 5th year of the children's life.

It is quite difficult to compare our analysis of the number of Phe blood tests with the results of other studies due to the different attitudes to research and organization of healthcare in various countries, as well as to the different ways of presenting the results. One of such studies was conducted over 1 year in 9 European countries and in Turkey.¹¹ Unfortunately, due to the low number of patients in the particular age groups in some of the analyzed countries (in 7 of the countries the surveyed group of children aged up to 1 year included 6 or fewer children), it is impossible to make accurate comparisons. While in the youngest age group (up to 1 year), the median number of blood tests even exceeded the recommendations, it decreased in subsequent periods. Moreover, since the study lasted for only 1 year, there was no follow-up data. In 2002, the results of the research performed in 4 PKU clinics in the UK and Australia¹² were published. The authors reviewed the available data from the years

1994–2000 in a group of 178 patients aged 0–4 years, and of 137 patients aged 5–9 years. The median percentage of following the recommendations regarding the number of Phe blood tests in the first 4 years of life was 81%, with the IQR 63–90%. For children aged 5–9 years, the median was 86%, and the IQR 58–113%. In our results for the Poznań center, the median for the first 5 years of life was 65%, with the IQR 44–84%. The same parameters for the 4-year period were respectively 67% (the median) and 46–86% (IQR). In 2004, Waitzman et al. presented the results of their analysis of the frequency of Phe blood tests in 59 patients aged 8 years in 4 PKU centers in the USA. The study covered the years 1980–1995.¹³ The researchers found that each week of delay in carrying out the Phe test increased the probability of exceeding the recommended Phe concentration by 10%. They also emphasized that the recommendations for test frequency issued by the US Medical Research Council Working Party on Phenylketonuria¹⁴ were not supported by any formal analysis. Viau et al.^{15,16} presented the results of a group of 55 patients, in which the average annual number of blood Phe samples was 16.5. The minimum value was 5 and the maximum was 62. Calculated according to this methodology, the average for the Poznań center was 26.7, with correspondingly lower maximum and higher minimum values.

In 2013, Hartnett et al.¹⁷ presented data on compliance to the recommendations regarding the number of Phe tests in a hospital in Vancouver, Canada. The median percentage of compliance in the first 6 months of life of the children was 98% (range: 74–125%), until the end of the 1st year – 87% (55–117%) and until 12 years of age – 90% (44–127%). One of the conclusions of the Canadian study was the following: “Concomitant with the increase in Phe levels, there was a reduced frequency of blood Phe monitoring as patients with PKU aged”.¹⁶ In the Poznań center, the median percentage of compliance in the 1st year was 90% (range: 19–140%). In 2011, Cotugno et al.¹⁸ observed a tendency in mothers with lower education to underestimate Phe in meals, resulting in missing the target Phe range. In their study of patients in Brazil, Vieira et al.¹⁹ considered the level of dietary compliance in patients up to 13 years old to be satisfactory if a patient's yearly median of Phe test results was lower than 6 mg%. It was found that 11 out of the 25 PKU patients in this group adhered to the diet.

In 1971, Acosta and Wenz²⁰ carried out an analysis of the diet adherence in a group of 101 PKU children. As an “excellent” result they defined 75% of the Phe blood levels within the target range of 2–6 mg%, as a “good” range – 75% of the blood levels within the range of 2–12 mg% and as “poor” – 75% of the Phe levels above 12 mg%. Noteworthy is the fact that the results do not cover the whole range of potential Phe values. The group with the best results included 49% of children under 1 year of age. The group with the worst results included 40% of children over 10 years of age. Children diagnosed early had better blood

test results. In 1996, Cabalska et al.²¹ stated that the results can be considered very good if Phe levels for at least 75% of the observation time are in the range of 4–6 mg%. The results of Phe were considered good if for at least 75% of the observation time they were included in the range of 6–12 mg%. Bad results were those of more than 12 mg% for 75% of the observation time.

German Collaborative Study of Children Treated for Phenylketonuria (PKU)²² in the group of 89 children as good results described those with a median of 4.3 mg% in the 1st and 2nd year of life, and 5 mg% in the 5th (there were 42 such children). In the intermediate group, 35 children were classified, with a median of 5 mg% in the 1st, 5.8 mg% in the 2nd and 7.4 mg% in the 5th year of life. Poor results of 12 children were those with a median of 5.6 mg% in the 1st year, 7.4 mg% in the 2nd and 10.7 mg% in the 5th year. The comparison of our results with the results of the German Collaborative Study is extremely difficult due to the passage of time and to the differences in target blood Phe. Our study showed that the blood Phe level defined in the German study as good was reached by 83% (44 out of 53) of Poznań patients in the 1st year of life, by 51% (27 out of 53) in the 2nd year and up to 43% in the 5th year. By comparison, the German results for the first 5 years of life were 46%. Overall, our results confirm the findings of the German Collaborative Study that in the 5th year of life more than 12% of patients have results that greatly diverge from those suggested in the recommendations. Somewhat thought-provoking in the German report was that results with a median over the recommended Phe levels given in the German recommendations, which is 4 mg%, were considered good.

Fisch et al.²³ presented data from a survey in 111 PKU clinics in the USA and Canada. In 20% of the surveyed hospitals, the non-compliance level was 20 mg%, in 13% of hospitals – 15 mg% and in 28% of hospitals – 10 mg%. In the 1st year of life, 43% of children had target Phe blood level under 5 mg%, and 51% – between 6 and 10 mg%. Van Spronsen et al.¹⁰ recommend out-of-the-ordinary intervention, such as increased intensity of monitoring or social worker supervision, if in patients under 12 years of age more than 50% of Phe concentrations are out of the target range for at least 6 months. Hartnett et al.¹⁷ presented the Phe test results from the years 1991–2009. The authors assumed that good Phe control was when more than 60% of Phe test results were within the treatment range (2–6 mg%); fair control – with 30–60% such results; and poor control – when less than 30% of Phe tests were within the treatment range. Of the 33 patients in the 1st year of life, 13 had good results, 16 – fair and 4 – poor. In the group from 2 to 6 years of age, 11 out of 29 patients had good results, 17 – fair and 1 – poor. In 12 patients (36%), the average concentration of Phe from the 2nd month of life to the end of the 1st year exceeded 6 mg%; till the 6th year of life 8 (26%) such patients were found. In the Poznań center, there were 15% (8 of 53) of children between 2 and 12 months of life with an average

Phe concentration higher than 6 mg%, 6 children (11%) had a good control and 21 (40%) – fair control. The difference was not statistically significant.

The major strength of this unique study is that all PKU patients remaining under care in our hospital were included. The majority of PKU studies comprised only a part of all patients remaining under care, which may have resulted in a significant bias, as it is more likely for researchers to have access to (and therefore include) patients who more strictly follow recommendations.

There are several limitations to this study. Firstly, we have studied the first 5 years of life, and therefore all the conclusions apply only to the 0–5 years age group. It would be desirable to expand the study onto older age groups of PKU patients as well. Secondly, our work focused on Phe concentrations in blood, the number of visits to a specialist and the number of blood tests, but we did not take into account the cognitive and intellectual functions, whose inclusion might have enriched the overall picture. Thirdly, the possibility cannot be excluded that patients implement the prescribed diet only shortly before blood sampling and that the Phe levels measured do not correspond to the real Phe values in the periods of time between tests.

In summary, the treatment control of PKU patients is the best in infancy, although many parents do not strictly follow the doctors' advice. In the next 4 years, over half of the patients fail to visit a specialist as many times as required, and even more fail to reach the recommended number of blood tests. Similar observations have been made regarding dietary compliance, as measured by Phe concentrations. In nearly half of the patients older than 12 months, similar percentages of correct and incorrect Phe concentrations have been detected. The process of control and therapy does not seem to depend on the level of education of the patient's parents, nor on their SES. Phenylalanine levels, however, remain correlated with the number of visits to a specialist and the number of Phe blood tests carried out.

Conclusions

Therapy effectiveness and patients' compliance in PKU is very good in infancy. However, both deteriorate in subsequent years. Moreover, they do not seem to depend on the family background. This reveals the need for systemic improvement of treatment control.

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References

- Blau N, Van Spronsen FJ, Levy HL. Phenylketonuria. *Lancet*. 2010; 376(9750):1417–1427.
- Blainey JD, Gulliford R. Phenylalanine-restricted diets in the treatment of phenylketonuria. *Arch Dis Child*. 1956;31(160):452–466.
- MacDonald A, Gokmen-Ozel H, van Rijn M, Burgard P. The reality of dietary compliance in the management of phenylketonuria. *J Inher Metab Dis*. 2010;33(6):665–670.
- Güttler F. Hyperphenylalaninemia: Diagnosis and classification of the various types of phenylalanine hydroxylase deficiency in childhood. *Acta Paediatr Scand Suppl*. 1980;280:1–80.
- Trefz FK, Schmidt H, Bartholome K, Mahle M, Mathis P, Pecht G. Differential diagnosis and significance of various hyperphenylalaninemias. In: Bickel H, Wachtel U, eds. *Inherited Diseases of Amino Acid Metabolism*. Stuttgart, West Germany: Georg Thieme Verlag KG; 1985:86–100.
- Phenylketonuria: Screening and Management. NIH Consensus Statement 2000 October 16–18;17:1–27.
- Management of PKU. A Consensus Document for the Diagnosis and Management of Children, Adolescents and Adults with Phenylketonuria. London, UK: The National Society for Phenylketonuria (UK) Ltd.; 2014.
- Burgard P, Bremer HJ, Bührdel P, et al. Rationale for the German recommendations for phenylalanine level control in phenylketonuria 1997. *Eur J Pediatr*. 1999;158(1):46–54.
- van Spronsen FJ, Ahring K, Gizewska M. PKU: What is daily practice in various centres in Europe? *J Inher Metab Dis*. 2009;32(1):58–64.
- van Spronsen FJ, van Wegberg AM, Ahring K, et al. Key European guidelines for the diagnosis and management of patients with phenylketonuria. *Lancet Diabetes Endocrinol*. 2017;5(9):743–756. doi:10.1016/S2213-8587(16)30320-5
- Ahring K, Bélanger-Quintana A, Dokoupil K, et al. Blood phenylalanine control in phenylketonuria: A survey of 10 European centres. *Eur J Clin Nutr*. 2011;65(2):275–278.
- Walter JH, White FJ, Hall SK, et al. How practical are recommendations for dietary control in phenylketonuria? *Lancet*. 2002;60(9326):55–57.
- Waitzman N, Bilginsoy C, Leonard CO, Ernst SL, Prince A. *The Effect of Phenylalanine Test Frequency on Management of Phenylketonuria (PKU)*. Working paper No: 2004-3. Salt Lake City, UT: University of Utah, Department of Economics; 2004.
- Recommendations on the dietary management of phenylketonuria. Report of Medical Research Council Working Party on Phenylketonuria. *Arch Dis Child*. 1993;68(3):426–427.
- Viau KS. *Correlation of Age-Specific Phenylalanine Levels on Intellectual Outcome in Patients with Phenylketonuria* [doctoral dissertation]. All Graduate Theses and Dissertations. Paper 739. Logan UT: Utah State University; 2010.
- Viau KS, Wengreen HJ, Ernst SL, Cantor NL, Furtado LV, Longo N. Correlation of age-specific phenylalanine levels with intellectual outcome in patients with phenylketonuria. *J Inher Metab Dis*. 2011;34(4):963–971.
- Hartnett C, Salvarinova-Zivkovic R, Yap-Todos E, et al. Long-term outcomes of blood phenylalanine concentrations in children with classical phenylketonuria. *Mol Genet Metab*. 2013;108(4):255–258.
- Cotugno G, Nicolò R, Cappelletti S, Goffredo BM, Vici Dionisi C, Di Ciommo V. Adherence to diet and quality of life in patients with phenylketonuria. *Acta Paediatr*. 2011;100(8):1144–1149.
- Vieira TA, Nalin T, Krug BC, Bittar CM, Netto CBO, Schwartz IVD. Adherence to treatment of phenylketonuria: A study in southern Brazilian patients. *J Inborn Errors Metab Screen*. 2015;3:1–7.
- Acosta PB, Wenz E. Nutrition in Phenylketonuria. In: Bickel H, Hudson FP, Woolf LE, eds. *Phenylketonuria and Some Other Inborn Errors of Amino Acid Metabolism*. Stuttgart, West Germany: Georg Thieme Verlag KG; 1971:181–96.
- Cabalska MB, Nowaczewska I, Sendek E, Zorska K. Longitudinal study on early diagnosis and treatment of phenylketonuria in Poland. *Eur J Pediatr*. 1996;155 (Suppl 1):S53–S55.
- Burgard P, Schmidt E, Rupp A, Schneider W, Bremer H. Intellectual development of the patients of the German Collaborative Study of children treated for phenylketonuria. *Eur J Pediatr*. 1996;55 (Suppl 1): S33–S38.
- Fisch RO, Matalon R, Weisberg S, Michals K. Phenylketonuria: Current dietary treatment practices in the United States and Canada. *J Am Coll Nutr*. 1997;16(2):147–151.