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RESEARCH REPORT

Dietary Habits and Metabolic Control in Adolescents and Young Adults with Phenylketonuria: Self-Imposed Protein Restriction May Be Harmful

A.M. Das · K. Goedecke · U. Meyer · N. Kanzelmeyer · S. Koch · S. Illsinger · T. Lücke · H. Hartmann · K. Lange · H. Lanfermann · L. Hoy · X.-Q. Ding

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Abstract Background: In untreated patients, phenylketonuria (PKU) results in severe encephalopathy with mental retardation. A protein-restricted diet is recommended which can be relaxed in adolescence/adulthood.

Methods: We contacted all 72 adult/adolescent PKU patients who had been treated in our center during early childhood. Some still regularly attended our outpatient clinics, while others were lost for follow-up, giving 51 patients in our study. We asked all patients to complete a dietary protocol as well as a questionnaire on quality of life. Blood and urine were analyzed and body impedance plethysmography and cerebral MRI were performed.

Results: 42 % of the patients followed protein restriction supplemented with amino acid mixtures (AAM), others had a vegan diet with (8 %) or without (14 %) AAM; 36 % said they were eating normally and did not need any AAM. However, based on dietary protocols and blood urea levels, protein intake was restricted in this patient group. None of the patients examined had serious nutritional deficits. Phenylalanine levels were higher in patients not taking AAM. MRI of the brain was not different from those following protein restriction and taking AAM. The lesions score and mood correlated best with the cumulative phenylalanine values during the first 10 years of life.

Conclusion: In summary, 50 % of adult/adolescent patients from our center did not take AAM at the start of our survey although they unknowingly followed self-imposed protein restriction. They had no overt nutritional deficits; however, long-term brain function may be compromised. Our study emphasizes the need for specialized metabolic care in PKU during adulthood.

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Competing interests: None declared

A.M. Das (✉)
Clinic for Pediatric Kidney-, Liver- and Metabolic Diseases, Hannover Medical School, Carl-Neuberg- Str. 1, D- 30625 Hannover, Germany
e-mail: das.anibh@mh-hannover.de

K. Goedecke · U. Meyer · N. Kanzelmeyer · S. Koch · S. Illsinger · T. Lücke · H. Hartmann
Clinic for Pediatric Kidney-, Liver- and Metabolic Diseases, Hannover Medical School, Hannover, Germany

K. Lange
Medical Psychology, Hannover Medical School, Hannover, Germany

H. Lanfermann · X.-Q. Ding
Institute of Diagnostic and Interventional Neuroradiology, Hannover Medical School, Hannover, Germany

L. Hoy
Institute for Biometrics, Hannover Medical School, Hannover, Germany

Introduction

Phenylketonuria (PKU, MIM #261600) is an inherited disorder of amino acid metabolism leading to the accumulation of phenylalanine and reduction of tyrosine in body fluids. If left untreated, patients develop severe encephalopathy with mental retardation and epilepsy. In many countries, PKU is diagnosed in the first days of life by newborn mass screening. Treatment is exclusively dietary, based on protein restriction supplemented with amino acid mixtures (AAM) free of phenylalanine (and enriched with tyrosine, vitamins, minerals, and trace elements) (Hendriksz and Walter 2004; Blau et al. 2010). Administration of tetrahydrobiopterin (BH4) has been suggested as an adjunct therapy in milder forms of PKU (Oddason et al. 2011), but its role in clinical medicine is still under discussion. "Diet for life" is advocated in this genetically determined disease,

although relaxation of the diet in adolescence and adulthood is thought possible (Burgard 2000; Abadie et al. 2005; de Baulny et al. 2007).

The latter may lead to at least partial loss of compliance, with consequent reduction in metabolic control. Some adult patients eat healthily, while others have an unbalanced diet not necessarily supplemented with an amino acid mixture. Still others may assume that their protein-restricted diet is normal as they are accustomed to protein restriction since early childhood. As a consequence, deficiencies of trace elements, vitamins, minerals, and amino acids may result because diet is not supplemented with AAM (Giovannini et al. 2007; Feillet and Agostoni 2010; MacDonald et al. 2011).

Symptoms of poor metabolic control are concentration deficits, abnormal behavior, and headaches, as well as general weakness, frequently accompanied by poor school or job performance (Hendriksz and Walter 2004; Blau et al. 2010). Skin and hair abnormalities may result from zinc or selenium deficiency.

Although major disabilities can be prevented by early protein restriction, more subtle deficits are common (Bick et al. 1993; Huijbregts et al. 2002; Anderson et al. 2007; Gentile et al. 2010), even in patients with good metabolic control. These health problems may be more pronounced in those patients who do not adhere to dietary recommendations and requirements.

In this study, we examined dietary habits and metabolic control in early-treated adult and adolescent patients, assessed their quality of life, and performed cerebral MRI.

Patients and Methods

Patients

All patients were recruited from one single center. PKU patients with other chronic diseases or chronic use of medication other than amino acid supplementation, pregnant women, and patients not diagnosed and treated in the newborn period were excluded. At the start of our study, 130 patients with PKU were registered in our center. We only invited adult/adolescent patients with classical, early-treated PKU to participate. This gave 72 adolescent and adult patients (45 females, 27 males) who regularly visited our metabolic outpatient clinic and/or were treated in our center as children or infants. Fifty-one PKU patients (age range 16–44 years, mean ± SD 26.6 ± 6.6 years; 32 females, 26.5 ± 6.2 years; 19 males, 26.8 ± 7.7 years) accepted our invitation.

Methods

Participants were asked to compile a dietary protocol, which was analyzed by our metabolic dietician. Additionally, we analyzed body composition and biochemical parameters in blood and urine which may indicate nutritional deficiencies, and offered cerebral MRI scans.

Not all 51 patients completed a dietary protocol. However, as many other parameters were measured, non-completion was not an exclusion criterion in our study.

Dietary protocol: Dietary protocols (3–8 days) were obtained from 36 patients (24 females, 12 males) at the start of our survey.

According to their nutritional habits, assessed by the patients and documented in the protocol, patients were divided into four groups:

1. Normal food (**"normal food"**)
2. Vegan without amino acid mixture **("vegan")**
3. Vegan with amino acid mixture (**"vegan + AAM")**
4. Protein reduced with amino acid mixture which is the recommended form of nutrition **("PKU-diet")**

All patients not taking AAM at the beginning of the study agreed to supplement their original diet with an AAM subsequently.

Body impedance analysis (BIA): BIA was performed using commercially available instrumentation (multifrequency impedance analyzer "Nutriguard-M", Nutriplus software, Data Input GmbH, Darmstadt, Germany). Contents of fat and water were analyzed. Furthermore, body cell mass, lean body mass, extracellular mass, and phase angle assessing the quality of cell membranes were approximated.

Biochemical analyses: At the beginning of our survey, parameters of organ function and nutritional status were determined in blood and urine (see Table 1 for an overview). Acylcarnitine profiles in dried blood were analyzed (assessment of carnitine status, fatty acid oxidation, organic acids) to exclude deficiency of vitamins and cofactors. Results were compared to normal values in our laboratory. Actual phenylalanine concentration in plasma was determined.

As therapeutic target concentrations of phenylalanine are age dependant, three age bands were chosen:

1. 0–10 years (target: < 4 mg/dl $= 240$ μM)
2. 10–15 years (target: < 15 mg/dl $= 900$ μM)
3. Older than 15 years (target: < 20 mg/dl $= 1{,}200$ μM)

Both average phenylalanine levels and variation of phenylalanine levels over lifetime are supposed to influence the outcome of the disease (Burgard 2000; Anastasoaie et al. 2008; Viau et al. 2011). Via retrospective statistical

Table 1 Overview of parameters analyzed in blood and urine

Blood	Parameters
Blood count	Leucocytes
	Thrombocytes
	Haemoglobine
	MCV
	MCH
Coagulation	Quick test
	INR Ratio
	PTT
Electrolytes	Potassium
	Sodium
	Calcium
	Chloride
	Phosphate
Bone	Alkaline phosphatase
Renal function	Urea
	Creatine
Liver function	AST
	ALT
	GLDH
	Alkaline phosphatase
	Gamma GT
	Cholinesterase
	Bilirubine
Additional	Glucose
Metabolic data	Lactate
	Creatine kinase
	Acylcarnitine profile
Iron metabolism	Iron
	Iron binding capacity
	Transferrin saturation
	Ferritin
Other trace elements	Zinc
	Selenium
Water-soluble vitamins	Folate
	Cobalamine
Liposoluble vitamins	Retinole
	Tocopherole
Protein metabolism	Protein
	Amino acids
Lipid metabolism	Cholesterol
Urine	
Organic acids	Methylmalonic acid and others
Additional data	Creatinine
	Albumine
	Alpha-1-microglobuline
	Amino acids

analysis mean phenylalanine concentration in plasma as well as variation of plasma phenylalanine levels during lifetime were calculated.

MR Imaging

Twenty-four out of 51 PKU patients included in the study underwent MRI examination of brain. The other patients did not give consent (claustrophobia, fear of pathological results, etc.) or had to be excluded for medical reasons (interfering material like dental brackets or tattoos).

MRI examinations were conducted using a 1.5 T scanner (Siemens Avanto, Erlangen, Germany). A routine MRI protocol was applied, which included single voxel spectroscopy (TR/TE = 6,000/20) in the parietal white matter.

MR morphological findings were independently interpreted by two experienced neuroradiologists. The images of all subjects were assessed using a standardized structured form (involvement of the lobar white matter (WM), periventricular white matter, centrum semiovale) and rated by using a modified version of the semiquantitative Scheltens scale (Scheltens et al. 1993).

Quality of Life, Mood Status, and Education

Health-related quality of life (HrQoL) and current psychological well-being were assessed using established psychometric questionnaires. The questionnaire "Alltagsleben (AL)" (Bullinger et al. 1993) consists of 45 items summed up to six subscales (general health perception, social role functioning, physical functioning, emotional role functioning, medical care, vitality). Psychological well-being was assessed using the "Profile of Mood States (POMS)" ((McNair et al. 1972), German (Biehl and Landauer 1975)) containing 35 items and four subscales of mood (vigor, irritability, fatigue, numbness). A separate item asked for the highest level of graduation.

Statistical Analysis

For statistical analysis, the IBM SPSS Statistics package 19 was applied (IBM corporation Armank, NY, USA). Data of the four subgroups were compared using the nonparametric Chi-Square test by Kruskal-Wallis to identify statistical significance. Differences were judged significant when $p < 0.05$ (95 % confidence interval).

For the correlation of phenylalanine levels versus MRI score and quality of life items, a Spearman-Rho test was performed.

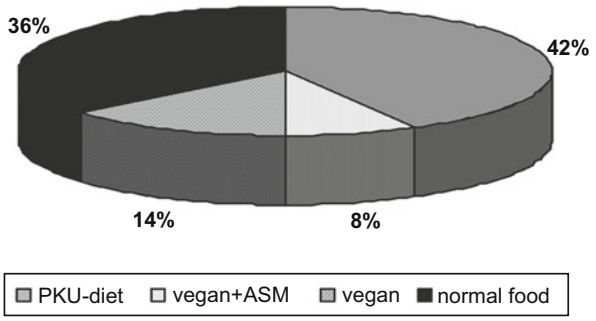

Fig. 1 Distribution of patients in dietary groups at start of the study, AAM = amino acid mixture

Results

The distribution of patients in the four different dietary groups at the start of our study is shown in Fig. 1.

Body mass indices (BMI) were normal in the two groups taking AAM and increased in the vegan (mean ± SD: 27.3 ± 4 kg/m^2) and normal food (25.9 ± 3 kg/m^2) groups, although differences were not significant ($p > 0.1$).

Dietary Protocols and Body Composition

Dietary protocol analysis at the beginning of the study is summarized in Table 2. In all patients, protein and energy intake were too low as judged by the DACH-recommendations (German-Austrian-Swiss dietary association) (DGE 2012). Protein supply was markedly reduced in patients following a vegan diet without AAM and in those who ate normally according to their personal judgment. Energy supply was also lower than recommended in these two groups. Results of follow-up dietary protocols showing normalized protein and energy intake after dietary intervention with AAM-supplementation can be found in Table 3.

Differences were found in the supply of phenylalanine. Patients who lived according to dietary recommendations had a lower intake than the other groups with more relaxed diets. In particular, patients in the normal food group consumed significantly more phenylalanine than vegan patients taking no AAM.

BIA-measurements (fat content, phase angle) were normal in all dietary groups, with no significant differences between groups. Compared to a normal, healthy population, no abnormalities were found for water, carbohydrate, and protein content (results not shown). Fat content in patients following a vegan diet was higher compared to patients following a protein-reduced diet or no diet at all. Body mass index and body cell mass were increased in vegan patients taking amino acids and reduced in vegan patients taking no AAM compared to patients following a diet supplemented with amino acids. Differences for these parameters were not significant. Membrane quality and cell density were not significantly different in the four subgroups as judged by the phase angle.

Biochemical Parameters in Blood and Urine

Although mean phenylalanine levels were within the therapeutic range in all groups, they were significantly higher in patients with presumed normal eating habits, $p < 0.05$ (Fig. 2). Historical data for phenylalanine levels are given in Fig. 3. There was a correlation between historical phenylalanine levels during childhood (0–15 years) and phenylalanine levels during adulthood (r = 0.6, $p < 0.01$, results not shown).

No systematic nutritional differences could be found between the four dietary groups except for levels of the amino acids phenylalanine and valine: patients who followed a strict protein-restricted diet with supplements had significantly lower concentrations of phenylalanine compared to those either without diet restriction or with vegan diets. Concentrations of valine were higher in patients following the recommended diet than in subjects consuming normal food.

Table 4 summarizes the results of the most important biochemical parameters in blood and urine. No statistical differences were found in blood cell count, coagulation, acylcarnitine profile in dried blood spots, organic acids in urine, concentrations of electrolytes, urea, creatine, lactate, glucose, creatine kinase, ALT, AST, GLDH, cholesterol, water- and fat-soluble vitamins, or trace elements such as iron, zinc, or selenium. However, there were single patients who returned to our outpatient clinic in response to the invitation for the study after many years without monitoring who had reduced levels of selenium and zinc. Interestingly, all patients had reduced or low normal urea concentrations in blood reflecting dietary protein restriction.

MRI Morphological Findings

None of the MRI scans showed signs of brain atrophy or signal changes in gray matter. Different grades of signal changes in white matter, typically found in PKU patients, were detected: while some of the patients showed no or only minor abnormalities, distinct signal changes in the parieto-occipital lobar WM and other brain regions were observed in other patients. The estimated semiquantitative Scheltens score varied from 0 (no changes) to 22. As an example, T2-weighted MRI scans of two patients are shown in Fig. 4 demonstrating enormous differences in white matter lesions. Linear regression showed a correlation between the retrospective mean phenylalanine levels in plasma and the lesion scores which was significant in the age period 0–10 years (R = 0.6, $p = 0.037$, Fig. 5). No differences between groups were observed.

Table 2 Supply of energy and basic nutrients at start of study compared to DACH-recommendations (2000) according to dietary protocol (DACH = German – Austrian – Swiss dietary association, * red: above recommended value, * green: below recommended value, AAM = amino acid mixture)

Diet	Total energy [kcal/day]	Carbohydrate [% of energy]	Fat [% of energy]	Protein [g/kg per day]
Protein-reduced with AAM	1830	61	24	1.1
Vegan with AAM	2169	57	31	0.9
Vegan without AAM	1605	57	35	0.5
Normal food	1400	56	34	0.6
DACH (2000)	> 2000	55-60	>30	1.0

Table 3 Follow-up: Supply of energy and basic nutrients compared to DACH-recommendations (2000) according to dietary protocol (* red: above recommended value, * green: below recommended value, AAM = amino acid mixture)

Diet	Total energy [kcal/day]	Carbohydrate [% of energy]	Fat [% of energy]	Protein [g/kg per day]
Protein-reduced with AAM	1716	61	22	1.0
Vegan with AAM	1720	62	25	1.0
Vegan without AAM	1519	54	32	0.7
Normal food	1558	57	28	1.0
DACH (2000)	> 2000	55-60	>30	1.0

Education, Quality of Life, and Mood

Educational performance was slightly better than average with 32 % of PKU patients reaching German secondary school diploma and only 2.6 % leaving school without qualification, compared to 30 % and 6 % in the general population, respectively. There were no significant differences between the dietary groups.

In all 51 patients, the questionnaire on HrQoL revealed no major deficits regarding general health perception, social role functioning, physical functioning, emotional role functioning, medical care, and vitality compared to the general population. Mood was correlated to the retrospective mean phenylalanine levels in the first 10 years of life ($R = 0.446$, $p = 0.037$) with better phenylalanine control leading to better mood. There were no significant differences in quality of life or mood assessment between the four dietary groups. Notably, the patients following the strict protein-restricted diet with amino acid supplementation did not feel worse than those with normal diet (according to their own assessment).

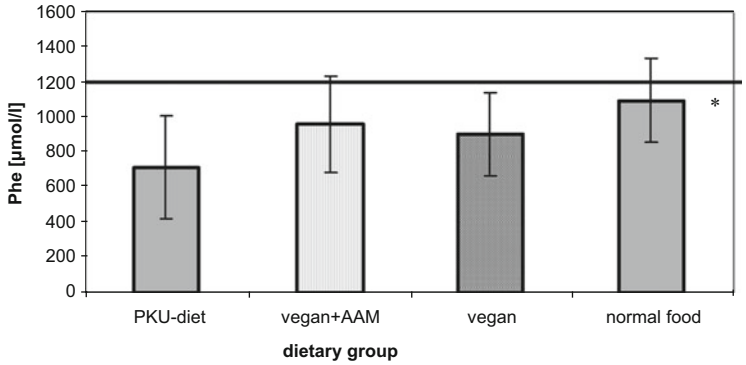

Fig. 2 Mean concentration of phenylalanine [µmol/l] compared to upper therapeutic levels for adults, * $p < 0.05$

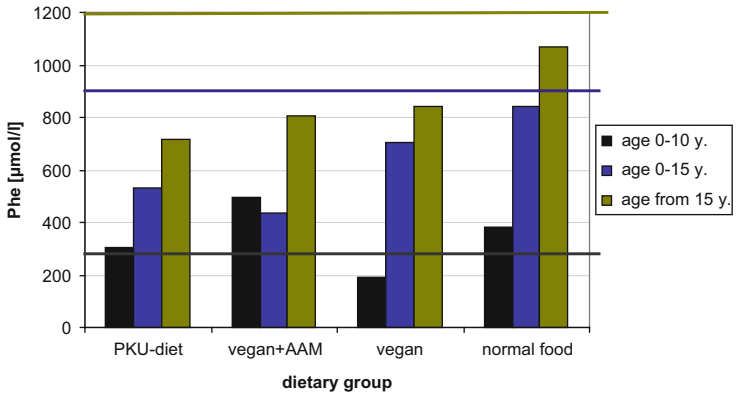

Fig. 3 Mean concentration of historical phenylalanine levels [µmol/l] compared with APS*-recommendations (1997) in three different age bands (*APS = German working group for pediatric metabolic diseases, APS- recommendations: 0–10 y.: 40–240 µmol/l, 10–15 years: 40–900 µmol/l, > 15 years: <1,200 µmol/l)

Discussion

"Diet for life" is recommended in classical PKU. While in the era of newborn screening dietary control is excellent during childhood, in most patients it can deteriorate during adolescence and adulthood (MacDonald et al. 2010). Transition from the pediatric clinic to an adult unit is known to be difficult (Feillet et al. 2010; Yoshino et al. 2010). A considerable number of adults (especially males) are lost for follow-up. Most women of childbearing age are aware of the risk of "maternal PKU" and regularly attend outpatient clinics, but older women – like many men – often think that dietary treatment is no longer necessary. Indeed, some older patients were previously advised by their doctors to discontinue the diet during adolescence and these patients frequently presume that they have normal eating habits. However, based on reduced or low normal urea levels in serum and dietary protocols in our survey, they continue a self-imposed reduction in protein intake. This is also true for the patient group following a vegan diet without AAM. Protein restriction in adulthood is related to that in early childhood, as we found a positive correlation between phenylalanine levels in both age bands.

Serious nutritional deficits may result when patients do not take amino acid supplements (MacDonald et al. 2011). In this study, serious nutritional deficiency was not found based on biochemical parameters in blood and urine. This does not completely rule out deficiencies in tissues. In previous studies on treated PKU patients, vitamin deficiencies (Hoeks et al. 2009) and low normal free carnitine values (Weigel et al. 2008) were found. An increased risk of vitamin B12-deficiency was reported in PKU patients on a relaxed diet in a previous study (Robinson et al. 2000); as methylmalonic acid in urine was negative, vitamin B12-deficiency could be ruled out in our cohort. We only identified reduced selenium and zinc levels in individual patients in the group with presumed normal eating habits without AAM. These rapidly normalized when amino acid mixtures were introduced.

Phenylalanine concentrations in blood were in the therapeutic range in all four groups indicating satisfactory metabolic control. However, phenylalanine levels were

Table 4 Selected biochemical parameters in the four groups, all were within normal range

Diet	Protein [g/l]	Urea [mM]	Tyrosine [μM]	Iron [μM]	Folate [μg/l]	Zinc [μM]	Selenium [μM]	Tocopherol [mg/dl]
Protein-reduced with AAM	73	3.3	58	19	14.1	10.2	0.74	10
Vegan with AAM	76	3.8	54	18	15.7	10.9	0.84	10
Vegan without AAM	76	3.6	56	17	11.2	9.9	0.70	9
Normal food	74	3.8	41	24	9.9	10.3	0.94	11
Reference range	**65–80**	**3.3–6.7**	**28–153**	**14–27**	**5.3–14.2**	**9.0–26.0**	**0.6–1.5**	**5–20**

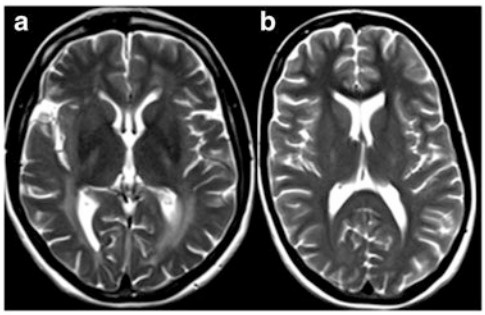

Fig. 4 Typical T2-weighted MRI scans of two PKU patients, where patient A shows diffuse white matter changes (Scheltens score = 10), patient B shows morphologically no white matter abnormalities

highest in those patients assuming to follow a normal diet. This may in principle be related to low energy supply in this group leading to catabolism. Elevation of branched chain amino acids can be used as an indicator of catabolism (Illsinger et al. 2005). However, as valine levels were lower in these patients, a catabolic state seems unlikely.

In line with other studies (Huemer et al. 2007), membrane quality and body composition do not seem to be compromised as judged by BIA-measurements; however, this is only an approximate overall estimation. Others have found correlations between (fat-free) muscle mass and protein intake (Huemer et al. 2007). As in other studies (Albersen et al. 2010; MacDonald et al. 2011), we saw a tendency to obesity in our cohort.

Despite early dietary treatment, MRI findings revealed typical white matter lesions of PKU as previously reported (Bick et al. 1993; Cleary and Walter 2001; Moller et al. 2003; Anderson et al. 2007; Leuzzi et al. 2007; Ding et al. 2008; Anderson and Leuzzi 2010) in many, but not all patients. In an attempt to quantify the white matter lesions, an adapted Scheltens score was used (Scheltens et al. 1993). As in other studies, the MRI lesions score could be correlated with cumulated retrospective phenylalanine levels during the first 10 years of life, while correlation with phenylalanine levels at later age bands was poor (Moller et al. 2003; Anastasoaie et al. 2008). T2-hyperintense white matter lesions are thought to be reversible as they are presumed to reflect intramyelinic edema (Leuzzi et al. 2007; Vermathen et al. 2007; Anderson and Leuzzi 2010). So far, follow-up MRI scans have only been performed in a few patients; therefore, reversibility of lesions in response to improved diet supplemented with AAM cannot be assessed at present.

On the functional level, mood was positively correlated with metabolic control during the first 10 years of life. Variation of phenylalanine levels over lifetime was reported to correlate with IQ (Waisbren et al. 2007; Anastasoaie et al. 2008); however, we could not find a significant correlation of variation of phenylalanine levels with white matter lesions. This indicates that other factors such as the blood-brain barrier or Phe-transporters (Moller et al. 2003) may influence the formation of white matter lesions. Further, secondary factors such as glucose metabolism may also play a role (Wasserstein et al. 2006). In line with these considerations, we did not detect differences in Scheltens' lesion score between the four dietary groups in our survey.

With regard to cognitive function, considerable executive and cognitive dysfunction even in early-treated PKU patients under good metabolic control has been described (Bick et al. 1993; Cleary and Walter 2001; Azadi et al. 2009; Gentile et al. 2010). Results from the questionnaires showed slightly better school performance of the PKU patients compared to the average population, which might be related to better self-management and structured lifestyle of PKU patients.

Quality of life was good. Patients not following a diet did not feel any better than patients on a strict diet with amino acid supplementation. However, the significance of this is limited due to the small sample size.

Previously it has been shown that compliance is not related to the knowledge of disease management in PKU patients (Durham-Shearer et al. 2008). In our view, the process of transition and patient management in the adult metabolic setting should be improved in order to maintain more adult patients on a diet supplemented with AAM.

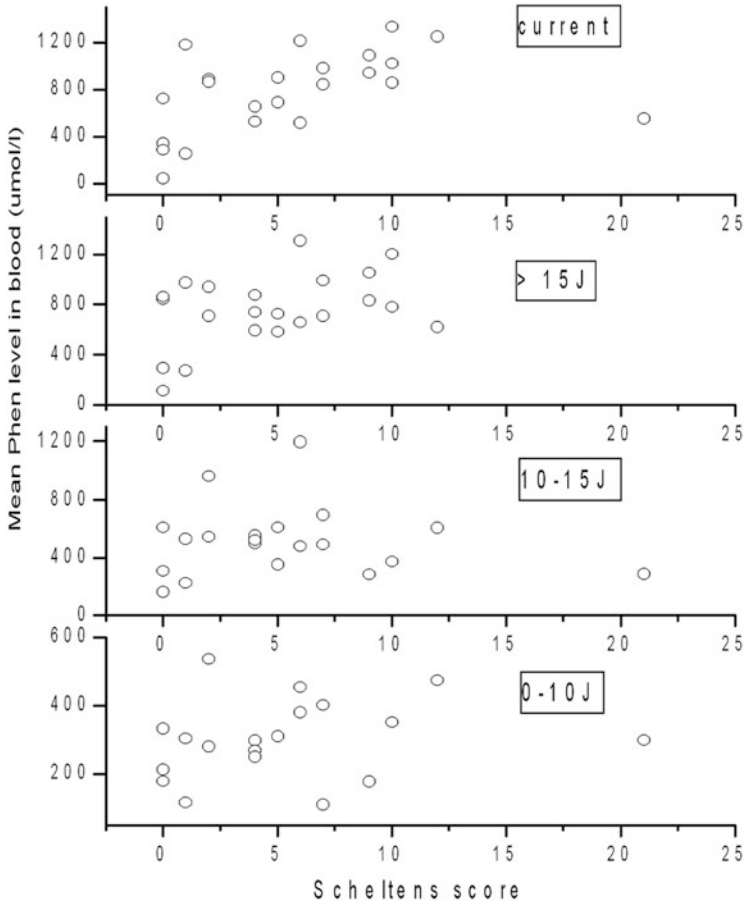

Fig. 5 Relationship between the cerebral lesions score and current as well as historical plasma phenylalanine levels at different age of the patients. There was a significant correlation for the age group 1–10 years (R = 0.6, $p = 0.037$), in all other age groups there were non-significant weak correlations (R = 0.1–0.4, $p = 0.43$–0.06)

Further, costs for AAM should be covered by health insurance companies, even for adults.

We are aware that the results obtained in this survey are of limited value as only a relatively small number of patients could be studied. However, examining patients from a single center had the advantage that patients were well known to us, and counseling, dietary recommendations, and therapeutic monitoring were relatively uniform. Results of our study may have implications for other metabolic diseases treated by protein restriction.

In summary, a considerable number of adult patients with PKU do not adhere to dietary recommendations including supplementation with AAM. Nevertheless, they unknowingly restrict their protein intake, probably as a result of following such a diet during infancy and childhood: protein-restricted eating habits are simply normal for them. Patients following a vegan diet without amino acid supplementation also have reduced protein and energy intake. This does not lead to significant deficits or overt functional deficiencies. However, it seems desirable over time to avoid even subtle nutritional deficits in order to prevent chronic intracellular "toxicity" or deficiency resulting in cellular dysfunction, especially of the brain. MRI lesions score and mood during adolescence/adulthood correlated with metabolic control during the first 10 years of life. There were no significant differences in MRI lesions scores between the different groups in our study population of adolescents/young adults. "Diet for life" does not only mean protein restriction but also supplementation with AAM and regular metabolic monitoring in adults by a unit with expertise in caring for patients with PKU/inborn errors of metabolism. A qualified metabolic dietician should be part of the team. Our study underpins the necessity of "Care for life" in patients with PKU including adequate funding.

Acknowledgment We thank Dr. G. Ulrich for advice regarding the quality-of-life questionnaires.

Take-Home Message

Adult patients with phenylketonuria tend to self-restrict their protein intake, irrespective of taking supplementary amino acid mixtures, and thus risk longer-term nutritional deficiency.

Compliance with Ethics Guidelines

The chairman of the local ethical review board decided that no vote was required as only routine procedures were carried out in order to monitor metabolic control.

Conflict of Interest

Anibh Martin Das, Kristin Goedecke, Uta Meyer, Nele Kanzelmeyer, Stefanie Koch, Sabine Illsinger, Thomas Lücke, Hans Hartmann, Karin Lange, Heinrich Lanfermann, Ludwig Hoy, and Xiao-Qi Ding declare that they have no conflict of interest.

Competing Interests

This study was financially supported by a grant of the German Ministry for Education and Research (BMBF) and by MetaX, Germany.

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