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METABOLIC DISEASES

P. Burgard · H. J. Bremer · P. Bührdel · P. C. Clemens
E. Mönch · H. Przyrembel · F. K. Trefz · K. Ullrich

Rationale for the German recommendations for phenylalanine level control in phenylketonuria 1997

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Abstract Treatment of hyperphenylalaninaemias due to phenylalanine hydroxylase deficiency with a low phenylalanine (Phe) diet is highly successful in preventing neurological impairment and mental retardation. There is consensus that, for an optimal outcome, treatment should start as early as possible, and that strict blood Phe level control is of primary importance during the first years of life, but for adolescent and adult patients international treatment recommendations show a great variability. A working party of the German Working Group for Metabolic Diseases has evaluated research results on IQ data, speech development, behavioural problems, educational progress, neuropsychological results, electroencephalography, magnetic resonance imaging, and clinical neurology. Based on the actual knowledge, recommendations were formulated with regard to indication of treatment, differential diagnosis, and Phe level control during different age periods. The development of the early-and-strictly-treated patient in middle and late adulthood still remains to be investigated. Therefore, the recommendations should be regarded as provisional and subject to future research. Efficient treatment of phenylketonuria has to go beyond recommendations for blood Phe level control and must include adequate dietary training, medical as well as psychological counselling of the patient and his family, and a protocol for monitoring outcome.

Conclusions Early-and-strictly-treated patients with phenylketonuria show an almost normal development. During the first 10 years treatment should aim at blood Phenylalanine levels between 40 and 240 μmol/L. After the age of 10, blood phenylalanine level control can be gradually relaxed. For reasons of possible unknown late sequelae, all patients should be followed up life-long.

Key words Phenylketonuria · Hyperphenylalaninaemia · Phenylalanine levels · Treatment recommendations

P. Burgard (✉)
Fachrichtung Psychologie,
Universität des Saarlandes, Im Stadtwald,
D-66123 Saarbrücken, Germany,
e-mail: p.burgard@cops.uni-sb.de,
Tel: +49-681-3022938, Fax: +49-681-3024792

H. J. Bremer
Universitäts-Kinderklinik Heidelberg,
Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany

P. Bührdel
Universität Leipzig, Univ.-Klinik für Kindermedizin,
Oststraße 21-25, D-04317 Leipzig, Germany

P. C. Clemens
Klinikum Schwerin Kinderklinik, Wismarsche Straße 397,
D-19049 Schwerin, Germany

E. Mönch
Virchow-Klinikum,
Medizinische Fakultät der Humboldt-Universität zu Berlin,
Augustenburger Platz 1, D-13344 Berlin

H. Przyrembel
Bundesinstitut für gesundheitlichen
Verbraucherschutz und Veterinärmedizin,
Postfach 330013,
D-14191 Berlin, Germany

F. K. Trefz
Kreiskrankenhaus Reutlingen Kinderklinik,
Steinenbergstrasse 31, D-72764 Reutlingen, Germany

K. Ullrich
Universitäts-Krankenhaus Eppendorf Kinderklinik,
Martinistrasse 52, D-20246 Hamburg, Germany

Abbreviations *BH_4* tetrahydrobiopterin · *CSPKU* collaborative study of PKU · *non-PKU HPA* non-PKU hyperphenylalaninaemia · *PAH* phenylalanine hydroxylase · *Phe* phenylalanine · *PET* positron emission tomography · *PKU* phenylketonuria · *VEP* visually evoked potentials

Introduction

Treatment of hyperphenylalaninaemias due to phenylalanine hydroxylase deficiency with a low phenylalanine (Phe) diet is a highly successful model of preventive paediatric medicine [51]. Systematic research and clinical observations have steadily increased our scientific knowledge as well as improved the outcome of treatment in Phenylketonuria (PKU McKusick 261600).

There is consensus amongst the workers in the field that for an optimal outcome, treatment should start as early as possible, and that strict blood Phe level control is of primary importance during the first years of life [51]. With regard to the decision for treatment, there is agreement that patients with classical PKU (Phe levels >1200 μmol/L (20 mg/dL) and mild PKU (600 μmol/L (10 mg/dL) $\leq$ Phe $\leq$ 1200 μmol/L (20 mg/dL) must be treated. There is only minor disagreement about treatment of non-PKU hyperphenylalaninaemia (non-PKU HPA), defined as Phe <600 μmol/L (10 mg/dL) while on a normal diet [15, 87, 88].

However, treatment policies for adolescent and adult patients show great variability. They range from the British policy of dietary treatment for life which aims at keeping Phe levels constantly below 700 μmol/L (11.5 mg/dL) to the French practice of discontinuing diet supplemented by amino acid mixtures at 5 years of age and thereafter only aiming at keeping blood levels below 1500 μmol/L [60]. In addition to conclusions drawn from single research results, national recommendations have only been published for Great Britain [43] and for Germany [73]. As shown in Table 1 these recommendations differ in many aspects.

It was the aim of a working party convened by the German Working Group for Metabolic Diseases to review current knowledge on hyperphenylalaninaemias due to Phe hydroxylase deficiency and to reformulate the present German recommendations for blood Phe level control. The British Medical Research Council Working Party on Phenylketonuria has justified the recommendations for Great Britain on the basis of research results on IQ data, speech development, behavioural problems, educational progress, neuropsychological results,

Table 1 Comparison of the British recommendations 1993 and the German recommendations formulated in 1990. (*Phe* phenylalanine)

British recommendations 1993 [43]		German recommendations 1990 [73]	
Age (years)	Phe levels	Phe levels	Age (years)
0			0
1			1
2	120–360 μmol/L	≤ 360 μmol/L	2
3	(2–6 mg/dL)	(≤ 6 mg/dL)	3
4			4
5			5
6			6
7			7
8			8
9			9
10	School age:		10
11	120–480 μmol/L	≤ 600 μmol/L	11
12	(2–8 mg/dL)	(≤ 10 mg/dL)	12
13			13
14			14
15		Individual recommendation	15
16		aiming at the maintenance of	16
17		intellectual efficiency and	17
18		psychological well-being	18
19			19
20	120–700 μmol/L	≤ 1200 μmol/L	20
.	(2–11.7 mg/dL)	(≤ 20 mg/dl)	.

electroencephalographic and evoked potentials, MRI, and abnormal neurological signs [42]. Our recommendations are based on the same variables.

IQ data

The analysis of longitudinal data from the British PKU Register revealed that Phe adversely influenced IQ until age 10, but not later on; infancy being the most vulnerable period [3, 70, 71]. The results of the US Collaborative Study of PKU (CSPKU) [2] and those of the German CSPKU [11] failed to demonstrate a significant effect of Phe levels after the age of 5 years on subsequent IQ development. In particular, a subsample of the German CSPKU with mean Phe levels of about 270 μmol/L during the first 5 years of life, and of 300 μmol/L (5 mg/dL) between 5 and 9 years, was no different from a healthy control group with regard to full-scale Wechsler IQ when tested at age 9 years. Subgroups with higher Phe levels during the first 5 years showed lower IQ scores already in their first IQ test at the age of 5 years but no progressive deterioration. Verbal IQs of a subsample of the German CSPKU with Phe levels ≤ 250 μmol/L (4.1 mg/dL) were significantly lower by 4 IQ points than those of a control group, both, however, with mean values above the population norm of 100. Patients of the British PKU Register showed an average longitudinal Phe level profile identical to the German CSPKU subsample with the highest levels (approaching 600 μmol/L (10 mg/dL) as early as 2 to 3 years. We have no explanation for the persistent negative influence of higher Phe levels on IQ scores after the age of 5 years in the British sample. For the age period from 10 years into adulthood the British results are mirrored in other studies [19, 64]. A subsample in the study by Schmidt et al. [64] with a mean annual Phe level of 250 μmol/L (4.1 mg/dL) until the age of 10 years did not show any negative trend in IQ development between adolescence and adulthood when Phe levels increased to an average of 900 μmol (15 mg/dl) at the age of 20 years. Patients with higher Phe levels during the first 5 years showed depressed but stable longitudinal IQ test profiles during adolescence.

Speech development

Melnick et al. [44] reported delayed speech development in PKU patients between 4 and 12 years compared with the test norms. In contrast, Ozanne et al. [48] found no significant differences between patients and matched controls. Although speech development was impaired in three patients with poor dietary control (90% of all Phe levels > 800 μmol/L (13.2 mg/dl)), paired comparisons between PKU children and their unaffected siblings from the US CSPKU did not show specific language deficits related to PKU [2]. Verbal fluency was no different between PKU patients and matched controls in a recent study on Scottish children and adults [20].

Behavioural problems

Compared with matched controls, 8-year-old patients from the British PKU Register showed significantly increased scores for hyperactivity and anxiety, predominantly in patients with mean Phe levels > 600 μmol/L (10 mg/dL) during their first 4 years of life and with low IQs [68, 69]. Personality questionnaire data of patients of the German CSPKU at the age of 8 years did not show substantial negative results [85]. Psychiatric interviews of 60 patients in the German CSPKU at the age of 13 years (mean Phe $level_{0-13\ years}$ = 500 μmol/L (8.3 mg/dL)) and their mothers showed an increase in mild behavioural or emotional disturbances by a factor of 1.5 compared to the normal sample. However, there was no need for psychiatric treatment [9]. Symptoms were not correlated with Phe levels and no PKU-specific behavioural pattern could be delineated. The same results were found in a study of adult patients [57].

Educational progress

Problems in educational progress have been reported for patients from the British Register [3], the US CSPKU [31], and French patients [1]. A subsample of the German CSPKU at the age of 12 years matched for sex and social class with healthy controls did not show differences in normal or special schooling, and numbers for repeated classes were not significantly different. Weglage et al. [84] found no differences in the school careers of 38 German PKU patients and their unaffected siblings. Comparison of the school grades of a sample of 51 young adult patients with those of their fathers revealed the common secular trend of better education in children and a distribution not significantly different from the data of the German population [64]. School careers of 20 early-treated Swiss patients were normal, too [65].

Neuropsychology

Table 2 lists the divergent results of 21 neuropsychological studies of PKU patients reviewed by Waisbren et al. [82]. The only consistent abnormality appears to be impaired choice reaction time. The divergent results can be explained by small sample sizes, lack of control groups, heterogeneity of age and of treatment history, insufficient control of intervening variables (e.g. IQ), and differences in test instruments.

A meta-analysis of choice reaction time studies with repeated measurement under low and high Phe levels [12, 32, 35, 62] revealed mean change of reaction time of 111 ms for mean Phe level change of 966 μmol/L. Phe level effects on reaction times were reversible irrespective of duration of periods without dietary treatment as well as patient's age and could be observed already 1 week after changing blood Phe levels. Compared with healthy

Table 2 Compilation of neuropsychological results in phenylketonuria (PKU) research (after [82])

Impaired functions	Intact functions
Higher cognitive skills, concept formation [50, 66]	School achievement, learning, speech [50]
Tactile-motor problem solving [7]	Pure motor tasks [29, 35]
Executive functions [17,89]	Executive functions [41]
Memory [17]	Memory [50, 89]
Simple reaction time [34]	Simple reaction time [66]
Choice reaction time [6, 10, 12, 32, 53, 62, 63]	
Sustained attention [6, 10, 63, 72]	Sustained attention [17, 18, 50]
Encoding of visual information [6, 8, 50]	Visual motor skills [36]

controls, mean choice reaction times were increased by 194 ms for children ≤ 10 years of age (mean concurrent Phe level = 558 μmol/L (9.2 mg/dL)), 82 ms for adolescents between 11 and 18 years (mean concurrent Phe level = 942 μmol/L (15.6 mg/dL)), and 159 ms for young adults between 17 and 25 years of age (mean concurrent Phe level 1146 μmol/L (18.9 mg/dL)). Cross-sectional control group studies have recently shown that after 5 to 10 years of strict treatment with Phe levels below 400 μmol/L, diet relaxations do not result in long-term progressive deterioration of reaction times [10, 20].

Studies testing the hypothesis of impaired executive functions presumably due to dopamine deficiency in the frontal lobes of patients were conducted with children younger than 6 years of age, adolescents, and young adults. Results for children are in line with IQ data and confirm the recommendation of therapeutic Phe levels below 360 μmol/L (6 mg/dL) during the first 5 years [16, 89]. However, results for adolescents and adults are patchy [20, 86]. A policy of minimising risks may be justified by the fact that synaptic density in the frontal cortex reaches maturity around the age of 16 years [28].

Electroencephalographic recordings and evoked potentials

Abnormal EEG findings such as general slowing and generalised paroxysmal activity with and without spikes increase with age but are not regarded as crucial for decisions about treatment [52]. Peaks of mean visually evoked potentials (VEP) were significantly prolonged in about 30% of patients with PKU but were uncorrelated with age at start of treatment, and not associated with clinical abnormalities, MRI scans or any parameter of biochemical control [4, 5, 38, 55]. Auditory evoked potentials in early-treated patients were normal [37].

Magnetic resonance imaging, magnetic resonance spectroscopy, and positron emission tomography

Abnormal signal intensity on MRI is most marked in the occipital-parietal regions and in more severe cases extends into the frontal and temporal lobes, basal ganglia, brainstem or the cerebellum [13, 55, 56, 79]. Partial reversibility after 2 to 3 months of continuous reduction of Phe levels below 360–900 μmol/L (6–15 mg/dL) has been observed irrespective of the interval off treatment preceding the scan [5, 13]. Abnormalities were significantly correlated with Phe levels during the time prior to imaging for concentrations between 600 and 1200 μmol/L (10–20 mg/dl), but not with Phe levels above 1200 μmol/L (20 mg/dL). MRI changes were not correlated with age at diet initiation or at MR examination, nor with electrophysiological results including VEP, neurological deficits, psychiatric problems and IQ. Neuropsychological variables and MRI scans show different temporal dynamics after Phe level variation and therefore are not expected to correlate with each other when Phe levels are controlled. There is little evidence that abnormal brain scans reflect neurological damage or are of clinical importance. Changes on MRI probably reflect a reversible structural defect of myelin rather than permanent demyelination [14]. The clinical relevance of position emission tomography (PET) studies also remains unknown.

MR spectroscopy yielded ratios of blood to brain Phe levels between 4/1 [54] and 2/1 [45]. Both values seem to be correlated only for blood Phe levels < 1200 μmol/L (20 mg/dL), possibly indicating a saturation of the carrier system at the blood-brain barrier when blood levels exceed 1200 μmol/L [30, 45]. Variations of brain influx and consumptions rates seem to be causative factors for the individual vulnerability to PKU [46].

PET studies showed a reduced protein synthesis rate for tyrosine when Phe levels were above 700 μmol/L (11.6 mg/dL) [49]. Recently, a reduction of regional brain glucose metabolism in regions of white matter changes could be demonstrated, but global cerebral glucose and oxygen metabolism were normal [25].

Abnormal neurological signs

Brisk tendon reflexes and tremor were reported to be frequent in older patients [13, 37, 67], but results for motor and sensory nerve conduction velocities are equivocal [13, 38]. Overt neuropathology (para- and quadriparesis, tremor, ataxia, epilepsy) was found in a few treated young adults [74, 81]. However, some of these patients had been treated late, had poor dietary control in infancy and none had a normal development during infancy and childhood. Clinical examinations of

51 adolescent and young adult patients who had been treated early and strictly showed no neurological abnormalities except for very discrete resting tremor and slightly brisk tendon reflexes of the lower limbs which were not associated with either MRI grading or biochemical control [4, 55]. A computerised test battery of fine motor behaviour demonstrated no significant differences between normal children, adolescents and adults and two patient groups on strict and relaxed diets matched for age and sex.

Non-phenylketonuria hyperphenylalaninaemia

Recommendations on the necessity for treatment of patients with non-PKU HPA seem to depend on the definition of this diagnosis. An IQ study from Great Britain [15] defining non-PKU HPA as Phe levels below 900 μmol/L (15 mg/dL) on a free diet concluded that all patients with Phe levels >360 μmol/L (6 mg/dL) on a normal diet should be treated. The German CSPKU defined non-PKU HPA as Phe levels <600 μmol/L (10 mg/dL) and found no significant differences between untreated cases and their unaffected siblings with regard to MRI, IQ, educational and professional progress, fine motor performance, and neuropsychological variables [87, 88]. The different results are possibly due to the inclusion of patients with Phe levels between 600 and 900 μmol/L (10 and 15 mg/dL) in the British sample.

Genotype-phenotype correlations

The genotype of the phenylalanine hydroxylase (PAH) locus can predict PAH activity, but other influences on transport and metabolism of Phe (e.g. variations of the transamination system, renal clearance of transamination metabolites) may account for differing metabolic phenotypes [75]. In addition, about 75% of all patients are compound heterozygotes and data on in vivo expression of both mutant genes do not exist. Residual enzyme activity predicted from *in vitro* studies [47] is correlated with pretreatment Phe levels, results of standardised protein challenges, and long-term fluctuation of plasma Phe levels, but not with success of mean Phe level control and intellectual development [33, 76]. Mutational analysis theoretically can replace the tetrahydrobiopterin (BH_4) test, but at present genotyping is primarily a scientific rather than clinical method. Only if residual enzyme activities are known for both allelic genotypes is information about genotype alone regarded as sufficient to decide about indication for treatment of PKU. In treated PKU patients PAH genotypes cannot predict intellectual outcome because it is mainly determined by the Phe levels during the first years of life, i.e. the quality of dietetic therapy, as well as other factors such as the family environment. It is also conceivable that hormonal and other metabolic effects may influence Phe homeostasis [78].

Late-treated patients

Almost all patients who have been treated late or who have experienced long periods of Phe levels far above the recommendations during their early years of life suffer from an irreversible but in most cases non-progressive intellectual impairment [58, 59]. In general, late treatment will have no effect on intellectual abilities, but in some cases neurological and behavioural symptoms can improve when Phe levels are brought below 600 μmol/L (10 mg/dL) for at least 3 months [23, 24, 27, 40, 74, 90].

Lower target value for blood phenylalanine level concentrations

For scientific purposes outcome variables are most often related to long-term indices of Phe control, where blood Phe levels are averaged over periods of several months or even years [61]. However, the compliance of individual patients is monitored on the basis of single blood Phe measurements. The actual blood Phe levels in the interval between two measurements in general remain unknown, and adolescent patients often adhere to a stricter diet before blood Phe levels are checked [83]. For clinical practice it seems reasonable to recommend an average compliance within the boundaries of the target values for Phe control. Possible adverse outcome effects of extremely low blood Phe levels have been debated for some time [21, 22, 39, 70]. In data from the British Phenylketonuria Register [70]. IQ fell by four points for each 5 months during which Phe concentrations were below 120 μmol/L. However, plasma Phe was analysed primarily by bacterial inhibition assays or paper chromatography, which do not measure precisely at low concentrations. MacDonald et al. [39] reported a negative correlation between the amount of Phe-free amino acid mixture consumed by the time of the evening meal and the pre-evening meal blood Phe level: 49% of the patients who had consumed at least two-thirds of their amino acid mixture by the time of the evening meal showed blood Phe levels below 100 μmol/L and a mean decrease of Phe levels of 40 μmol/L from the times pre-breakfast to pre-evening meal. There was a positive correlation between the amount of amino acids taken by the time of the evening meal and the overnight increase in blood Phe levels. The authors consider this a potential risk for adverse effects of too low Phe levels during periods of unknown length of a day when dietetic control is monitored by pre-breakfast levels only. However, Phe levels were not analysed with regard to the daily pattern of Phe intake, and pre-evening levels did not include Phe intake of the evening meal. Unfortunately minimal pre-breakfast levels are not reported in the publication and cannot be extrapolated from the data. Although 9 of 19 patients showed a large variation in their daily Phe intake (up to 300% in one patient) as well as in their Phe blood levels, no correlation was found for the whole

group between the intake of protein and Phe on the one hand and pre-breakfast, pre-evening meal Phe levels or daily changes in Phe levels on the other. In contrast, van Spronsen et al. [80] demonstrated a rise in plasma Phe levels after standardized breakfasts up to 145% (mean 116%) of the pre-breakfast levels in eight classical PKU patients, and no significant decreases in plasma Phe levels until 2 h after a subsequent standardized lunch. Prolonged overnight fasting increased plasma Phe levels to a mean of 123% of the initial pre-breakfast level. The authors concluded that the timing of blood sampling is not a significant factor for the monitoring of PKU treatment. Güttler et al. [21] have suggested that an overnight rise in Phe levels in PKU patients could be due to net protein catabolism and release of Phe into the plasma amino acid pool. However, when protein anabolism during the day is predominating (as in healthy children) children should thrive well. There are no data which demonstrate that, given a sufficient and balanced intake of all essential nutrients and energy, Phe blood levels in the physiological range, measured by precise quantitative methods, are dangerous for the patient's development. The lower limit for the recommended range of plasma Phe levels in PKU patients is therefore set at the same level as for normal persons, i.e. 40 μmol/L.

In conclusion, on the basis of our present knowledge about the relation between treatment and outcome in PKU, the German working party has come to the following conclusions:

1. The development of intellectual abilities measured by IQ tests is normal when dietary treatment starts during the first weeks of life and Phe levels are ≤ 240 μmol/L. After the age of 10 years, IQ does not deteriorate even in children with suboptimal Phe level control during infancy and childhood. Educational and professional careers are normal in early- and strictly-treated patients.

2. Early- and strictly-treated patients are not at risk for psychiatric disturbances necessitating psychiatric care or psychotherapy.

3. Overt neurological signs of clinical relevance have so far not been observed in early-treated patients. Electrophysiological, MRI and PET studies do not give clear answers to questions concerning treatment recommendations.

4. Neuropsychological investigations demonstrate that Phe levels affect reaction times at all ages; however, the influence is reversible and non-progressive. The clinical relevance of neuropsychological data is not clear, in particular the validity of the frontal lobe dopamine deficiency hypothesis remains uncertain.

5. Patients with non-PKU HPA (Phe levels < 600 μmol/L (10 mg/dL)) need no treatment.

6. DNA analysis of the PAH gene can contribute to differential diagnosis but does not predict the outcome of treated patients.

7. Patients treated early and strictly during the first decade are not at known risk for neurological and/or mental symptoms of clinical/practical significance even when in subsequent years Phe levels may reach 1500 μmol/L (25 mg/dL).

8. The question when dietary treatment of adequately-treated patients can or should be relaxed or discontinued is unresolved. It is also not proven that long-term dietary treatment is completely without health risks, nor that it is harmful for patients' health [91].

Although, actual scientific knowledge provides no firm recommendation for long-term treatment of PKU, for clinical practice it is necessary to base therapy on current evidence. Deducing from these conclusions we recommend the following treatment policies. Recommendations for the treatment of maternal PKU have been published elsewhere [77].

Recommendations for treatment

1. Patients with HPA due to PAH deficiency with blood Phe levels ≥ 600 μmol/L (10 mg/dL) on a normal diet must be treated with a low Phe diet including a Phe-free protein or amino acid supplement. The diagnosis has to be determined by Phe tolerance, genotyping or *ex juvantibus* by blood Phe levels during periods of metabolic instability. When necessary, diagnosis should be verified by a standardised load test.

2. After confirmation of diagnosis, dietary treatment aimed at maintaining blood Phe levels between 40 and 240 μmol/L (0.7–4 mg/dL) has to be initiated as early as possible after birth and should be maintained until the age of 10 years.

3. Between 10 and 15 years of age blood Phe level control can be gradually relaxed to upper levels of 900 μmol/L (15 mg/dL).

4. After the age of 15 years Phe levels should be kept ≤ 1200 μmol/L (20 mg/dL). Woman planning a pregnancy and expectant mothers should be treated according the recommendations for maternal PKU [77].

5. Continuation of strict Phe control should be offered to patients whose treatment has been suboptimal with regard to diet initiation or quality of Phe level control during infancy and childhood, or who show impairment or overt symptoms.

6. Patients older than 10 years showing neurological symptoms or neuropsychological, intellectual or behavioural abnormalities should continue as strict as possible dietary control except when these symptoms have an aetiology unrelated to PKU.

7. Dietary relaxation should be monitored by clinical, neurological, intellectual and neuropsychological follow up in order to secure physical health, intellectual efficiency and psychological balance. Patients should be assessed at least once a year even after diet discontinuation.

8. Untreated and late-treated patients suffering from severe retardation and impairments can show behavioural improvement after dietary reduction of blood Phe levels to below 600 μmol/L (10 mg/dL). Test trials should last at least for 6 months.

Table 3 The German Phe level recommendations for PKU 1997

Age period	Phe levels	Age (years)	Phe monitoring	Clinical monitoring[1]
		0	Weekly to fortnightly	At least quarterly
		1		
		2		
		3		
< 10.0 years	40–240 μmol/L	4	Fortnightly to	Every 3–6 months
	(0.7–4 mg/dL)	5	monthly	
		6		
		7		
		8		
		9		
		10		
		11		
10.0 years	40–900 μmol/L	12	Monthly	Every 6 months
−15.0 years	(0.7–15 mg/dL)	13		
		14		
		15		
		16		
> 15.0 years	40–1200 μmol/L	17	Every 2–3 months	Every 6–12 months
	(0.7–20 mg/dL)	18		
		19		
		.		

[1] Diet, physical growth, neurological and psychological development, general state of health

Table 3 summarises the recommendations for blood Phe levels.

The history of PKU research has taught us that dietetic Phe level control is a highly efficient policy of preventive paediatric care and the amount of Phe in the blood during the first years of life is a powerful predictor of outcome in patients. However, despite great scientific and clinical efforts the pathogenesis of the disease is not well understood, and the development of the early- and strictly-treated, i.e. clinically healthy, patient, in middle and late adulthood still remains to be investigated. Therefore, our recommendations should be regarded as provisional and subject to corroboration or refutation by future research. Finally we would like to stress that efficient treatment of PKU has to go beyond recommendations for blood Phe level control and must include adequate dietary training, medical as well as psychological counselling of the patient and his family, and a protocol for monitoring outcome [26].

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