Eur J Pediatr (1987) 146 [Suppl 1]: A17–A19

European Journal of
Pediatrics

Continuation vs discontinuation of low-phenylalanine diet in PKU adolescents

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Key words: Phenylketonuria – Adolescents – Dietary control – Intelligence – Psychological problems

Introduction

To investigate the question of continuation versus discontinuation of low-Phe diet, the development of 52 adolescents and young adults with PKU was analysed. The study is retrospective and is based on follow-up of PKU patients collected during a 23-year period from the Heidelberg clinic – the oldest patient was born in 1963, the youngest in 1974. Because of the long observation period, a number of people were involved in the treatment and examination of these patients (see Acknowledgements).

Patients

Fifty-two patients (23 males, 29 females) satisfied the following criteria: Phe level above 20 mg/dl on a normal diet, no defect in the cofactor system, onset of dietary treatment during the first 3 months after birth (mean time of diet inception 39 days). Nine patients for whom important information was missing were not included in the study. All 52 patients were older than 12 years, 15 older than 18 years, at the close of the study.

Methods and results

For the last 10 years our policy of treating children with PKU has been the following: Strict Phe-reduced diet with resulting target Phe blood levels of 2–4 mg/dl up to the age of 10 years; a somewhat relaxed diet with levels of 10–12 mg/dl up to the age of 15 years, or older if possible; above the age of 15, protein-restricted diet with target Phe levels of 15–20 mg/dl. Ten years ago some patients were put on a protein-restricted diet at the age of 8. At no time, however, it has been recommended to discontinue the diet completely. Table 1 shows how the 52 adolescents managed their diet.

In summary, up to the age of 15 our diet prescriptions were accepted by most patients, whereas over the age of 18 almost half the young adults opted for a slightly restricted normal diet.

The Phe blood levels of the patients on a diet were determined using the semiquantitative Guthrie test and checked at half-year intervals using column chromatography. The Guthrie tests were performed weekly or 2-weekly for the first year, subsequently on a monthly basis. Controls became more irregular as the patients became older. Patients whose Phe levels were frequently above 12 mg/dl, were checked more often, using column chromatography. The median of the measured Phe values for each patient was computed on a 6-monthly basis, resulting in two values a year. The means of the medians of all patients are shown in Fig. 1.

The mean Phe value of the whole group increased over the 20-year observation period. Figure 1 shows that the mean Phe level at 10 rose to 10 mg/dl. At age 15 the Phe level equals

Table 1. Diet management of the 52 PKU patients at different ages

Age (years)	Group				Total
	1	2	3	4	
12	41	11	—	—	52
15–16	19	14	2	3	38
≥18	1	6	1	7	15

1, Phe-low diet plus amino acid mixture; 2, protein-restricted diet plus amino acid mixture; 3, protein-restricted diet without amino acid mixture; 4, normal diet without excessive protein intake

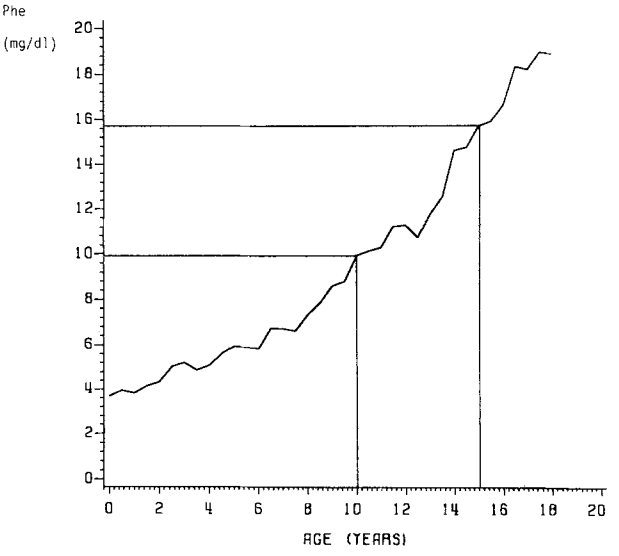

Fig. 1. Mean Phe level of all patients according to age

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Abbreviations: Phe = phenylalanine; PKU = phenylketonuria; IQ = intelligence quotient; HAWIK = Hamburg-Wechsler-Intelligenztest für Kinder; HAWIE = Hamburg-Wechsler-Intelligenztest für Erwachsene (German versions of WISC and WAIS)

Table 2. IQ scores of all patients at different ages

	Age (years), IQ tests					
	4–5 Binet-Kramer	6–7 Binet-Kramer, HAWIK	8–9 Binet-Kramer, HAWIK	10–13 HAWIK, HAWIK-R	14–16 HAWIK, HAWIK-R, HAWIE	16 HAWIE
n	51	50	48	47	38	12
Full IQ (SD)	104 (10)	105 (13)	108 (16)	109 (13)	111 (14)	112 (9)
Verbal IQ (SD)	—	—	—	106 (12)	112 (10)	113 (12)
Performance IQ (SD)	—	—	—	108 (14)	110 (15)	111 (9)

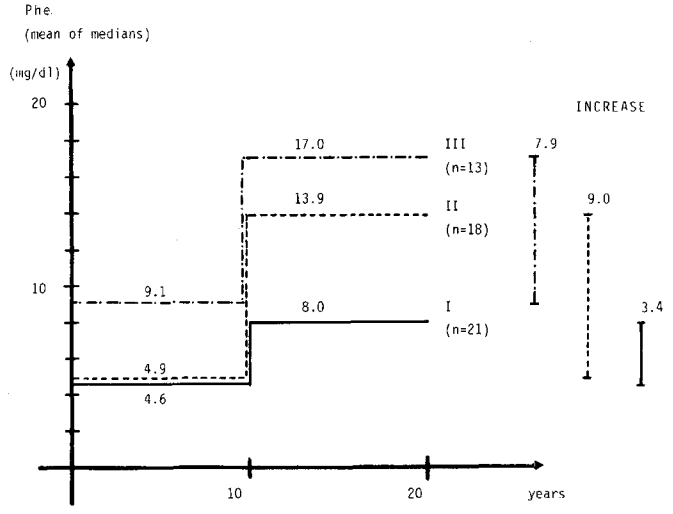

Fig. 2. Classification of patients into three groups according to their Phe levels below and above 10 years of age

Table 3. IQ scores in the three groups of patients. Figures in parentheses represent number of patients

Group	Age years					
	4–5	6–7	8–9	10–13	14–16	>16
I	108 (20)	110 (19)	118 (20)	117 (19)	124 (11)	—
II	103 (18)	105 (18)	107 (17)	106 (18)	111 (17)	113 (9)
III	99 (13)	97 (13)	91 (11)	99 (10)	97 (10)	—
Total	104 (51)	105 (50)	108 (48)	109 (47)	111 (38)	112 (9)

15 mg/dl, which seems to be a critical threshold value in determining the outcome of the development of younger children, as was shown in the US Collaborative Study [3].

As a measure of the effect of the treatment, intelligence scales were used to determine each patient's intellectual performance. Tests were carried out every 2–3 years, beginning at preschool age. Due to the considerable length of time over which investigations were done, a variety of tests were used. The Binet-Kramer was applied mainly in the preschool age group, the Hamburg-Wechsler Intelligence Scales (HAWIK and HAWIE) in schoolchildren and young adults. Since 1984 the children have been tested with the revised form of the HAWIK (HAWIK-R) [2]. This HAWIK-R is known to lead to IQ scores up to 15 points below the scores found when using the HAWIK. Comparability of IQ was achieved by transforming the HAWIK-R scores on the basis of linear regression analysis using data from a comparison between HAWIK and HAWIK-R in a class of elementary schoolchildren.

Group means and standard deviations of the IQs in all age-groups are within the normal range (Table 2). There is even a slight IQ increase with time; this effect will be discussed later. So far no decrease of IQ can be seen in connection with the increasing Phe blood levels. There is no consistent difference between verbal and performance IQ over the age of 10.

Evaluating the results of all patients as a group still does not answer the question of whether dietary changes have an influence on intellectual development in adolescents. Therefore we analysed the data in a different way by subdividing patients into groups according to Phe blood levels. First, patients were chosen who had maintained good dietary control for the first 10 years of life. Good dietary control was defined by Phe levels below 7.1 mg/dl. Thirty-nine patients fulfilled this criterion. These patients were further divided into two groups according to the rise of mean Phe levels over the age of 10 years.

All patients were expected to show a rise in Phe blood levels from age 10 onwards corresponding to a change in diet recommendations. In the period from age 10 to the close of the study, group I shows an increase of mean Phe blood values of 3.4 mg/dl, with the initial mean Phe level of 4.6 mg/dl rising to 8.0 mg/dl. Group II shows an increase of mean Phe blood level of 9.0 mg/dl, with an initial mean Phe level of 4.9 mg/dl rising to 13.9 mg/dl. Group III comprises the remaining 13 patients with an elevated initial mean Phe level of 9.1 mg/dl rising to 17.0 mg/dl, an increase of 7.9 mg/dl (Fig. 2).

Assuming Phe blood concentrations have an effect on intellectual performance, no difference would be expected between group I and II up to the age of 10 years, and group I would have a more favourable course of intellectual development than group II above the age of 10. Group III would be expected to have a less favourable intellectual development before age 10 and a further deterioration of performance above the age of 10 compared to groups I and II.

Table 3 shows the IQs of the observed groups at different ages. Contrary to our hypothesis there is an increase in IQ with increasing age in both group I and group II, and no apparent deterioration in group III. It is questionable whether

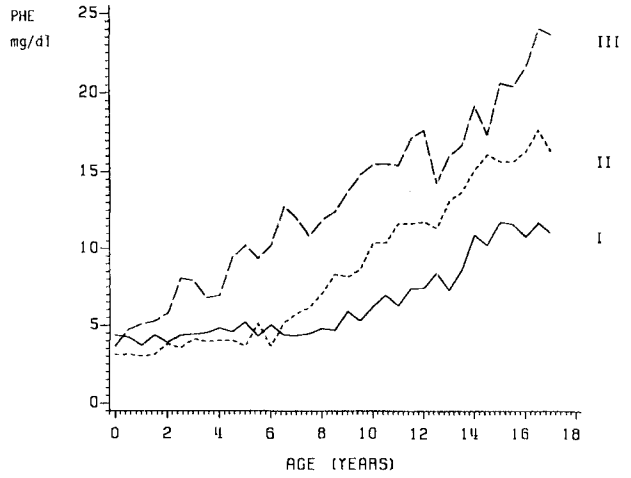

Fig. 3. Mean Phe levels of the three groups of patients according to age

this positive change reflects a true rise in intellectual performance. There are at least three arguments which have to be taken into consideration, and which have been discussed in previous longitudinal studies [1]: (1) A learning effect by test repetition. (2) An overall increase in standards of education during the last 20 years, resulting in a shift of test norms. This argument is particularly relevant for the HAWIE, the test used in young adults. (3) A "true" improvement of intellectual performance of at least a subgroup of patients whose educational training has been above average due to their PKU.

Further results can be obtained by comparing the three groups in detail. The mean IQs rise faster in group I than in group II. Between the ages of 4 and 7 years – the time when Phe level ranges in both groups are comparably low – the mean IQ in group I is already somewhat higher than in group II; this difference increases with age, becomes significant at the age of 8–9 years and reaches a maximum at the age of 15. In group III, with poor dietary control below age 10 and a rise of Phe levels to over 15 mg/dl above age 10, mean IQ levels remain constant over the whole observation period. The fact that group III shows no IQ increase may in fact reflect a deterioration in intellectual performance which is hidden by the effects described above. As expected, there is a correlation between the Phe blood level and the intellectual performances in the three groups above the age of 10. Interestingly, group I and II already differ at age 8–9 years. Looking at the course of Phe blood levels in both groups over the years, it becomes evident that the mean Phe blood level in group II already begins to increase at age 6 (Fig. 3). Possibly, this explains the early difference in intelligence between the two groups.

Discussion and conclusions

In light of these results, strict dietary treatment seems to be successful. However, during frequent and intensive contact with the patients we learned a lot about the psychological problems arising from having to maintain a strict diet and from suffering from a chronic disease known to effect mental functions. Up to now, this subject has not been systematically investigated in adolescents. Nevertheless, we feel it is important to report on our observations so far. The most frequent conflicts are caused by separation and individuation. Although young adolescents wish to escape from parental dietary control, they find it very hard to accept the responsibility for keeping to the PKU diet. Whereas children identify PKU with dietary prescriptions given by parents and physicians, adolescents are able to understand that PKU is a severe chronic disease. As an inborn disorder, potentially causing mental deficiency, PKU upsets the still vulnerable balance of identity in young adults. The majority of our older patients tend to protect themselves by denying their handicap. These inner conflicts can lead to depressive moods, lack of self-confidence and a tendency to postpone separation from parents.

In summary, data on development of intelligence show that the quality of dietary control in later childhood and adolescence is important for intellectual outcome. Whereas the mean IQ score of the whole group remains in the normal range throughout the observation period, differences only become evident on comparing groups of patients with different dietary control. The importance of other factors – independent of the Phe blood level – on the development of intelligence must still be determined. These factors may include the extent of enzyme deficiency, parents' intelligence and psychosocial effects.

The results of this study seem to justify the continuation of a Phe-restricted diet until early adulthood using Phe-free amino acid mixtures to satisfy protein requirements. Compliance in continuation of the Pre-restricted diet is more difficult to achieve in adolescence than in childhood. Our experience has taught us that patients require not only medical care, but also educational training and psychological support.

Acknowledgements. This study was supported by the Bundesministerium für Forschung und Technologie (BMFT). The following persons were involved in the treatment and examination of the patients. Pediatrics: H. Bickel, H. Schmidt; psychology: S. Grubel-Kaiser, H. Jurisch-Homm, U. Michel; dietetics: E. Müller, L. Schürrle; biochemistry: E. Harms, P. Lutz, D. Matthias, E. Schmid-Rüter, F. K. Trefz; data analysis: M. Mahle, D. Noschka, P. Teuschel, J. Pietz (alphabetical order of names). We are grateful to Dr. K. Boehnke for making his HAWIK-R data available to us.

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