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Intelligence and professional career in young adults treated early for phenylketonuria

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Abstract The intellectual status and professional careers of 51 young adults with phenylketonuria whose treatment started before 3 months of age are described. Their mean IQ was 97 (SD = 16). Of the IQs, 4% were more than 2 SD below the norm. The distribution of types of schooling of the patients was comparable to that in the German population. The professional careers of nearly all the patients were according to their educational level. Within the sample the outcome was significantly correlated with phenylalanine (Phe) control, even when the patients' social background was statistically taken into account. The main influence of Phe on intelligence seems to occur during the first decade of life since IQ data remain stable even after Phe levels increased during adolescence.

Key words Phenylketonuria · Intelligence · Education · Professional career · Phenylalanine control

Abbreviations *Phe* phenylalanine · *PKU* phenylketonuria

Introduction

The high risk of becoming severely mentally and physically handicapped for patients with phenylketonuria (PKU) can be prevented efficiently by the early introduction of a diet low in phenylalanine (Phe). While there is no doubt that treatment has to be continued until late childhood, it is not clear whether the diet can be relaxed or stopped in adolescence or adulthood [1, 4, 6, 10–13, 16, 17]. To answer this question, data on the development of adults with PKU who have been receiving treatment for PKU since infancy are of particular importance. In the literature, there are many reports concerning the intellectual development and progress in school [1–3, 8, 18]; however, the evaluation of the professional careers of adults is almost lacking [5]. Horst Bickel started treatment of a group of PKU patients in Germany in the early 1960s. Therefore, thanks to him, we are able to present data on the intelligence, education and professional careers of 51 now adult patients.

Patients and methods

The 51 patients were born between 1963 and 1974. Their mean age was 25 (19–31) years. They were classified as classical PKU, having blood Phe levels above 1200 μmol/l on a normal diet. Diet inception started within 3 months after birth (mean 39 days). Phe intake was calculated according to the recommended blood Phe concentration. Table 1 shows that over the years the recommendations concerning the target for blood Phe level concentrations became stricter. However, because the absolute differences in the recommended Phe levels were not very large, the sample was not divided a priori into two treatment groups.

The Phe-restricted diet of the patients was supplemented with various Phe free formulas which changed in composition over the decades. The influence of these different formulas on the developmental outcome was not investigated because the consequences of different degrees of Phe control was the prime focus in this study, and the sample size did not allow us to consider another variable in the statistical model.

The patients had been recommended to receive weekly control of Phe during the 1st year of life, every 2 weeks from 2 to 4 years and at least once a month after the age of 4 years. Blood samples were analysed with the Guthrie test and regularly checked by column chromatography. From 1977 on, column chromatography was

Table 1 Recommendations for target Phe concentrations at different ages

Until 1976/77	0–8,0 years 120–240 (< 360) μmol/l	8,1–15 years 720–900 μmol/l	after 15 years < 1200 μmol/l
Since 1977	0–10,0 years 120–240 (< 360) μmol/l	10,1–15 years < 600 μmol/l	after 15 years ≤ 900 μmol/l

used as the routine method. As a measure of dietary control for each patient the Phe median of each year was calculated up to the age of 20 years. Beyond this age period the data were incomplete, either because the patients had not yet reached the older ages or because their data were missing. By cluster analysis of the 20 yearly Phe medians, the whole sample was divided into different groups of Phe control [7]. Intelligence was tested with the German version of the Wechsler Intelligence Scale for Children (WISC and WISC-R) and the Wechsler Intelligence Scale for Adults (WAIS and WAIS-R). Unrevised test results were transformed into revised scores using linear transformations according to the instructions given by the test authors [15]. Age for testing was not completely standardized in this sample. Therefore the different ages were divided into three age groups: late childhood and early adolescence (10–13 years), adolescence (14–15 years), and adulthood (16–30 years). Where more than one IQ test was available for a given age period, the mean of the test results was calculated. None of the patients had overt neurological symptoms. Because a direct comparison with the educational systems of other countries is not possible, the types of schools are indicated in German. The "Abitur" is comparable with the "A levels" in Great Britain and prepares students for university. "Hauptschule" and "Realschule" are types of secondary education (9 and 10 years of schooling), while a "Sonderschule" corresponds to a special school for children with learning disabilities. In addition the actual status of the professional careers was recorded. Since IQs for the patients' parents were not available, father's level of education was introduced into the analysis.

Results

Cluster analysis of the longitudinal Phe profiles revealed three subgroups of dietary control (Fig. 1), indicated as cluster of "good", "intermediate" and "poor" dietary control. The good cluster had Phe control in accordance with the recommendations given after 1977 (see Table 1). Ten patients started to lose dietary control after the 4th year of life. The patients who were given a relaxed diet from age 8 years onwards are included in the "intermediate" cluster. The partition of the sample into three groups was a result of the recommendations on the one side and the patients' compliance on the other.

Figure 2 shows the mean longitudinal IQ values from early adolescence up to adulthood allocated to the three Phe clusters. On average, patients with the lowest Phe levels had the highest IQs and vice versa. Time of diet inception (t) showed no significant influence on the IQ results ($r_{t*IQ\ 10-13} = -0.18$, NS; $r_{t*IQ\ 14-15} = -0.21$, NS; $r_{t*IQ\ 16-30} = -0.15$, NS), probably due to reduced variance in this sample. A repeated measurement analysis of variance of the IQs (three test times↔three clusters) revealed a significant main effect for cluster ($F(2.37) = 9.17$, $P < 0.001$). The mean IQ of the "good" cluster differed significantly from that in the poor cluster ($F(1.25) = 13.15$, $P < 0.001$) and also from that in the "intermediate" cluster ($F(1.30) = 10.65$, $P < 0.01$). The "intermediate" cluster was not significantly different from the "poor" cluster ($F(1.19) = 1.56$, NS). The main effect for time was significant ($F(2.74) = 5.06$, $P < 0.01$), due to a subtle but constant increase of the mean IQ over time. However, a non-significant interaction cluster-by time ($F(4.72) = 1,53$, NS) indicated similar mean IQ changes over time for all the three Phe clusters. In adulthood the mean IQ of the total sample was 97 (sd = 16; range = 61–131). The IQs of two patients were two SD below the norm with values of 61 and 69.

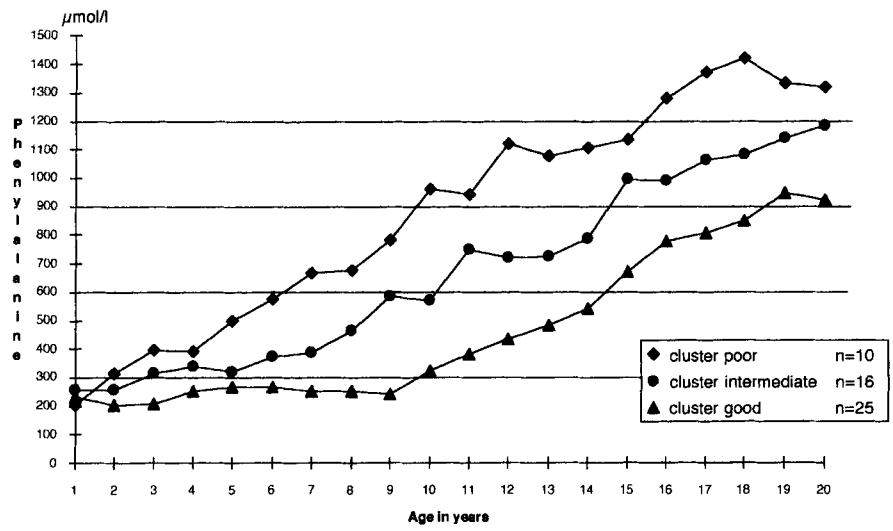

Fig. 1 Three groups of dietary control separated by cluster analysis

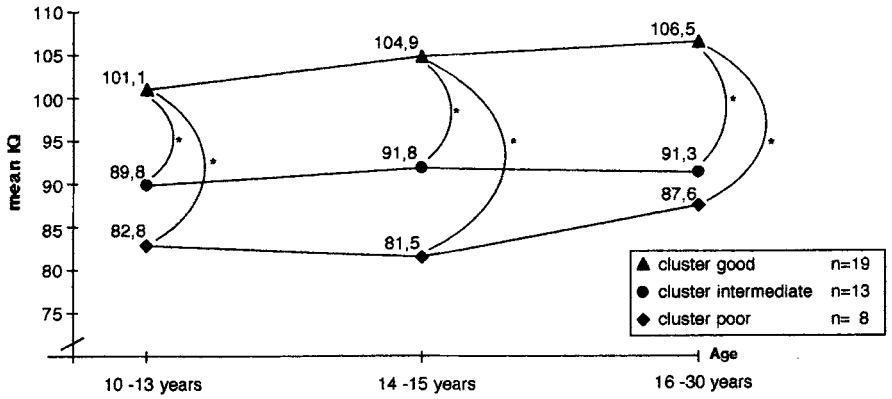

Fig. 2 Longitudinal IQs of three Phe clusters, * $P < 0.05$

Table 2 School grades of patients (divided by clusters) and their fathers

School grade	Fathers (n = 51)	Patients (n = 51)	Cluster		
			good	intermediate	poor
Abitur	6	12	10	1	1
Realschule	13	22	14	7	1
Hauptschule	32	16	1	8	7
Sonderschule	0	1	0	0	1

Table 2 shows school grades of the 51 patients and their fathers. As in the general population the educational status of the patients was higher than that of their fathers. Apart from one patient who, because of learning disabilities, attended a special school, all patients finished school successfully. The distribution of school types attended by our study sample was not different from that of the normal German population ($\chi^2(2) = 2.36$, NS) [14].

The correlation between type of schooling and the three Phe clusters was highly significant (phi = 0.7, $P < 0.001$, Table 2). The correlations between father's education (fe) patient's education (pe) and Phe cluster were $r_{fe*pe} = 0.45$ ($P < 0.01$, $n = 48$), $r_{fe*phe} = 0.22$ (ns, $n = 48$), $r_{pe*phe} = 0.62$ ($P < 0.001$, $n = 48$). As to be expected on the basis of general population data, there was a significant correlation between the education of the fathers and their offspring. The correlation between the father's education and the Phe cluster was not significant. The correlation between Phe control and patient's education was highly significant. Controlling for father's education (fe) the correlation between Phe and the patient's educational level (pe) increased the numerical value to $r_{phe*pe.fe} = 0.73$, $P < 0.001$.

School success was also reflected in the professional careers of the patients. Nine were university students, seven were training for a profession or an occupation, 31 were already employed according to their training, three were employed without any special training (one of them refused occupational training, having an IQ of 120), and one patient had a compulsive neurosis and so far was not able to be trained. All the female patients had finished or were actually training for an occupation in contrast to their mothers,who were frequently housewives.

Discussion

The results on this sample of patients – seven of whom had severely retarded siblings who were not treated – again demonstrates the efficiency of PKU treatment. The patients exhibited normal physical development, their IQs were in the normal range and corresponded to their social background. With regard to education and professional careers the sample does not appear to differ from the normal population. Apart from the one person with a compulsive neurosis, all patients are able to live independently without any special support. However, within the sample the outcome was significantly correlated with Phe control, even when the patient's social background was statistically taken into account. The mean IQ of the cluster "good" in adulthood was 107. On average the median Phe concentrations were below 300 µmol/l up to the age of 10 years, below 600 µmol/l up to 15 years and later about 900 µmol/l, reflecting excellent dietary control according to the recommendations. Adults in the cluster "poor" had a mean IQ of 88 with Phe levels exceeding the recommended levels from the age of 4 years. Although the mean Phe levels of all three clusters increased over the second decade of the patients' lives, the mean IQs did not deteriorate. The increasing mean IQ over time, which was responsible for the significant main effect, probably was a result of test sophistication.

Even though half of the patients had high blood Phe concentrations, they managed their school and professional training programmes successfully. This would indicate that the essential influence of dietary control must

have happened during the first 10 years of life. However, since the relative positions of the three clusters remained stable, our data do not give information about the possible consequences of Phe levels above 1200 µmol/l for the cluster "good". On the other hand, the mean IQ of the cluster "good" remained stable despite 600 µmol/l increase of Phe levels after the age of 10 years. Thus it can be assumed that a moderately relaxed diet during adolescence and adulthood, as we have recommended to our patients, has no adverse consequences for intelligence development.

Further evidence on the influence of dietary control on IQ results and on school career can be derived by comparing our patients with a sample from the the British PKU register, which covers similar ages [2]. The cluster "poor" runs nearly parallel to the 50th percentile of the British sample, with Phe concentrations even lower during the first 5 years. This might explain the 27% of IQs 2 SDS below the norm in the British sample compared with 4% in our sample, and 2% in the normal population.

Our data might suggest that a low Phe diet could be relaxed or even terminated after late childhood. However, an influence of high Phe blood concentrations on intellectual performance during adolescence and adulthood cannot be excluded completely. A neuropsychological study including a subgroup of our adult patients has demonstrated that information processing and sustained attention could be improved by lowering the Phe blood level from 1200 to 600 µmol/l [9].

Our group of adults achieved a normal intellectual development and normal careers. This success was significantly determined by the quality of dietary control. From early adolescence onwards, no significant influence of Phe on Wechsler IQ scores could be detected. However, a definite decision concerning dietary control during adolescence and adulthood can not be made on the basis of these data. Finally the problem of late effects, after the patients have reached a greater age, remains to be investigated.

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