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Intellectual development of the patients of the German Collaborative Study of children treated for phenylketonuria

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Abstract In a multicentric and interdisciplinary approach the German Collaborative Study of Children Treated for Phenylketonuria (PKU) investigates prospectively the effects of early started strict dietary treatment on the growth and development of 140 patients. The present paper focuses on longitudinal intelligence data from 4, 5 and 9 years of age of 89 patients in relation to the quality of dietary control in comparison to 200 healthy children tested by the same protocol. Cluster analysis of phenylalanine (Phe) levels distinguished a cluster of good dietary control with Phe levels according to the recommendation of maintaining Phe levels below 360 µmol/l, a cluster of poor dietary control with Phe levels greater than 600 µmol/l after the age of 3 years, and a cluster of intermediate control. Intelligence quotients (IQ) and Phe clusters were inversely related with non-significant differences between the clusters good and intermediate. On average, all three clusters scored significantly lower than healthy age peers. Mean IQ scores decreased for patients as well as for healthy children due to different tests used at different measurement occasions. Patients with poor dietary control showed a steeper decrease between 4 and 5 years than patients with better dietary control. Between 5 and 9 years IQ differences between patients and healthy children remained stable. Verbal IQs were higher than performance IQs for patients as well as for healthy children. It is concluded that after early and strict treatment during the pre-school years Phe levels, in the range observed, do not influence IQ development until the age of 9 years. IQ subscale pattern indicate that PKU results in a generalized reduction of IQ instead of disturbing specific abilities. It remains to be investigated whether higher Phe levels are also innocuous and/or may result in late effects.

Key words Phenylketonuria · Dietary treatment · Phenylalanine recommendations · Intelligence development

Abbreviations *CMMS* Columbia Mental Maturity Scale · *IQ* intelligence quotient · *Phe* phenylalanine · *PKU* phenylketonuria · *WISC-R* Wechsler Intelligence Scale for Children – Revised · *WPPSI* Wechsler Preschool and Primary Scale of Intelligence

Introduction

From the early start of research on phenylketonuria (PKU) intelligence has been regarded as an important variable measuring the outcome of the disease and evaluating different treatment policies. Imbecillitas phenylpyruvica, a term coined by Følling [8], consists of a clinically obvious severe mental and behavioural retardation which can be diagnosed easily. However, there are also reports of persons with PKU with normal intelligence [13, 17, 18]. After the introduction of early started treatment with a strictly low intake of phenylalanine (Phe), short-term as well as long-term sequelae became more and more subtle, and clinical evaluations had to be supplemented or even substituted by psychometric intelligence scales [26] and computerized neuropsychological tests [27].

Based on the recent knowledge of diagnosis and treatment of PKU and the very first experiences of the US Collaborative Study [31] in 1976 Bickel, together with a group of physicians and psychologists, inaugurated the German Collaborative Study of PKU as a multicentric and interdisciplinary prospective project to investigate the development of PKU patients [12]. In this study, it was recommended to keep blood Phe levels below 360 µmol/l during the first 10 years of life. This recommendation, at that time very strict, can nowadays be found in general recommendations for treating PKU [15, 25]. Details of the design and protocol as well of results have been reported elsewhere [3, 5, 19, 21–23, 28] and in the present issue of the European Journal of Pediatrics. The data presented in this paper concentrate on the development of intelligence of the patients from 4 to 9 years of life in relation to their blood Phe levels during the first 9 years of life. Furthermore, the assumption that, as far as neurotransmitters are involved, elevated blood Phe levels interfere with the structure and function of the brain [10, 11], thereby effecting primarily those parts of intelligence that rely on problem solving abilities, i.e. adaptation to new situations and less on culturally skilled judgment habits [4, 14], was investigated.

Patients and methods

Eighty-nine patients of German origin (48 girls; 41 boys) born between 1978 and 1984 who had reached the age of 9 years and for whom longitudinal IQ results of the ages of 4, 6, and 9 years were available, were included in the analysis. Treatment started at a mean age of 16 days (range 4–45 days). The aim of the dietary management was to maintain plasma Phe concentrations in the range between 120 and 360 µmol/l. Phe level monitoring was recommended every 2 weeks during the 1st year of life, later on once a month. According to a standardized protein challenge with 180 mg Phe/kg body weight and day at the age of 5 months 80 patients were classified as classical PKU (type I: Phe levels > 1200 µmol/l), and nine were classified as milder PKU (type II: blood Phe levels > 600 µmol/l and ≤ 1260 µmol/l) [2, 12]. Over the years, in some patients compliance decreased with regard to reduced Phe intake and/or to the frequency of Phe level control. For each patient and each period of 12 months the yearly medians of all measured Phe levels were computed as an index of dietary control.

IQ was tested at 4 years with the Columbia Mental Maturity Scale (CMMS), at 6 years with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), and at 9 years with the Wechsler Intelligence Scale for Children – Revised (WISC-R). The WPPSI and the WISC-R differentiate between verbal and performance intelligence. The subtests of the verbal scale focus on the accumulated sociocultural experience, whereas the performance subscale might be considered as measuring the child's immediate problem solving abilities and capacity to apply past experience to new situations. Some of them have also to be solved under time limits introducing the component of mental speed [20]. It was hypothesized that performance IQ should be smaller than verbal IQ and that the differences between both should be associated with the level of Phe control. A sample of healthy children, born between 1980 and 1981 and participating in the Munich Longitudinal Study on the Genesis of Individual Competencies (LOGIC) [29], was tested with the same IQ tests at the same ages at approximately the same times as the patients. These data permit skipping the issues of different test norms and training effects associated with repeated measurements [7, 9, 24].

Results

The profiles of the first 9 yearly medians were grouped by cluster analysis in three homogeneous clusters [19], labelled as good, intermediate, and poor dietary control (Fig. 1). On the average nearly half of the patients succeeded in maintaining their Phe levels below the upper threshold of the recommendation indicating good dietary control. About 40% of the sample was in the cluster intermediate and had Phe levels greater than 360 µmol/l after the 2nd year of life, ending up at a mean level of 540 µmol/l at the age of 9 years. The cluster poor, comprising 12 patients, lost dietary control already after the 1st year of life, passed the 600 µmol/l value at the age of 4, and reached nearly 840 µmol/l at the age of 9 years. The strategy of clustering longitudinal profiles of medians was corroborated by correlational analysis of the nine medians. Apart from medians at 1 and 2 years, which are poor predictors of later quality of dietary control, all other medians showed correlation coefficients greater than 0.50 (e.g. $r_{med3*med9} = 0.54$), indicating that the position of individual patients in the rank order of all patients was highly stable. The three clusters neither differed substantially in age at starting treatment (cluster good: $\bar{x} = 16{,}4$ days, SD = 6.5; cluster intermediate: $\bar{x} = 15{,}3$ days, SD = 7.0; cluster poor: $\bar{x} = 14{,}9$ days, SD = 3.8) nor were they associated with the type of PKU ($\chi^2(df = 2) = 0{,}124$, ns), which started treatment nearly at the same time (type I: $\bar{x} = 15{,}6$ days, SD = 6.5; type II: $\bar{x} = 17{,}7$, SD = 5,7). IQ measures were neither correlated with type of PKU nor with age at start of treatment. The mean IQ profiles of the three measurement occasions for the three clusters showed an inverse pattern to the degree of dietary control (Fig. 2). Analysis of variance for repeated measure-

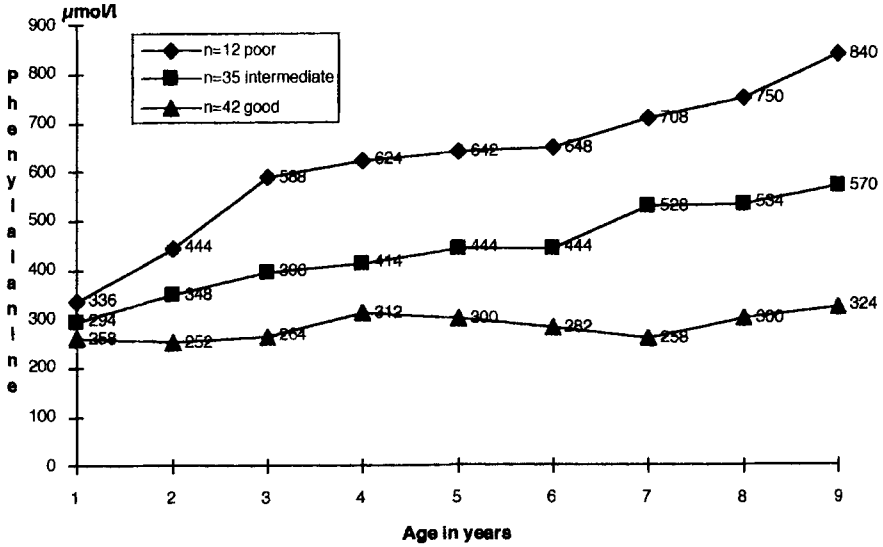

Fig. 1 Profiles of the first nine yearly medians for three clusters of good, intermediate, and poor dietary control

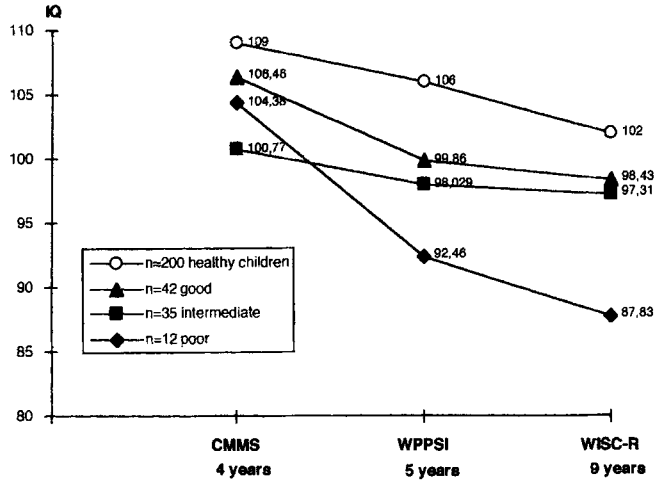

Fig. 2 Mean IQ profiles of three measurement occasions for three Phe clusters and healthy age mates

ments (3 clusters × 3 test times) revealed a non significant effect for cluster (F (2,86) = 2,0, ns), a significant effect for test time (F (2,172) = 22,17, $P < 0.0001$), and a significant interaction cluster by time (F (4,172) = 2,94, $P < 0.05$). One-way analyses of variance testing the differences between clusters for the three IQ measurements only revealed a trend for the WISC-R results at 9 years (F(2,86) = 2,74, $P < 0.07$). Correlations of IQ test results with yearly medians were almost zero for Phe levels during the first 2 years. CMMS IQ at the age of 4 years was independent of Phe control at any time preceding the test. IQ at the age of 5 significantly correlated with the Phe median 3 ($r = -0.21$, $P < 0.05$), whereas IQ at age 9 correlated significantly with median 4 ($r = -0.30$, $P < 0.01$), and medians 6–8 ($r = -0.25$, $P < 0.05$; $r = -0.22$, $P < 0.05$; $r = -0.27$, $P < 0.01$). However, all these correlations dropped to non significance after eliminating the cluster poor from the analysis. Parallel to the results of the quality of dietary control the three IQ measurements were highly correlated to each other ($r_{IQ3*IQ5} = 0.46$, $P < 0.0001$, $r_{IQ3*IQ9} = 0.44$, $P < 0.0001$, $r_{IQ5*IQ9} = 0.76$, $P < 0.0001$).

Results of one-tailed t-tests of the differences between healthy children and patients are reported in Table 1. Starting with the age of 5 years mean IQs differed significantly from healthy children for all three clusters. The results of the verbal and performance subscales at the ages of 5 and 9 years for the three Phe clusters and healthy controls are shown in Fig. 3. Subscale patterns were the same for patients of all three clusters as well as healthy peers, level differences found for global IQ were reproducible on the subscale level.

Table 1 One-tailed t-tests of IQ results for three Phe clusters and healthy children

	IQ 3 years	IQ 5 years	IQ 9 years
Cluster good versus healthy children	$t(df = 225) = -1,23$	$t(df = 249) = -2,68$**	$t(df = 141) = -1,78$*
Cluster intermediate versus healthy children	$t(df = 218) = -3,64$***	$t(df = 242) = -3,29$***	$t(df = 134) = -2,31$*
Cluster poor versus healthy children	$t(df = 195) = -1,30$	$t(df = 219) = -3,32$***	$t(df = 111) = -4,70$***

*** $P < 0.001$
** $P < 0.01$
* $P < 0.05$

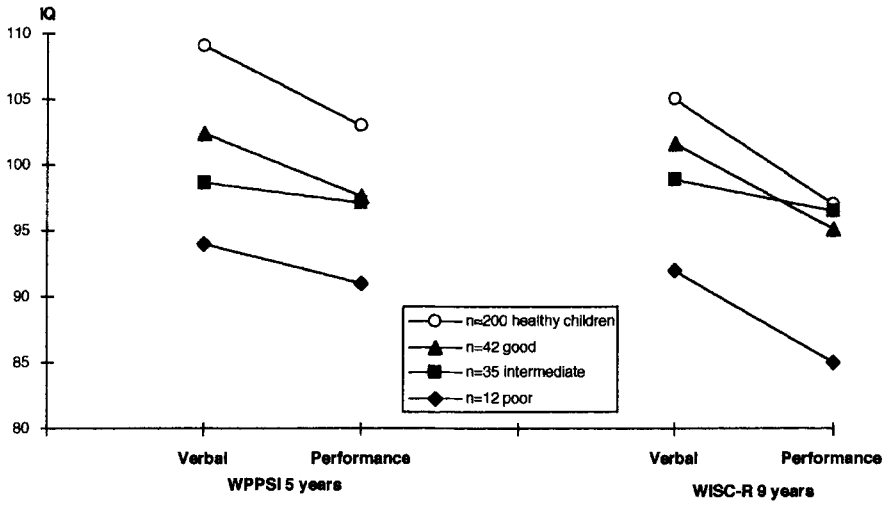

Fig. 3 Verbal and performance IQs at 5 and 9 years of age for three Phe clusters and healthy controls

Discussion

On the level of yearly medians the recommendation of keeping blood Phe levels below 360 µmol/l could be achieved by about half of our subjects and resulted in IQ scores in the normal range. However, there were still significant differences to healthy controls after the age of 3 years. Full scale IQs were not significantly different for the clusters of good and intermediate dietary control. The data of the cluster poor demonstrate that 600 µmol/l is an upper threshold for Phe levels too liberal for pre-school years. The mean IQ score of these patients was 10 points below the scores of healthy children as well as patients who grew up with lower blood Phe levels. The mean IQ of the patients in the cluster intermediate who transgressed the recommended Phe level of 360 µmol/l already before school entrance did not deteriorate and remained stable for the period between 5 and 9 years although their Phe levels steadily increased to a level of nearly 600 µmol/l at the time of the last measurement. The British Medical Research Council Working Party on Phenylketonuria [15] has recommended Phe levels below 360 µmol/l until the age of 6 years and Phe levels below 480 µmol/l and not greater than 720 µmol/l until the age of 10 years. Our patients in the cluster intermediate meet these recommendations at the upper limit and their IQ test results might indicate that they could be given a greater Phe tolerance during their school years. However, our neuropsychological results [Schmidt, Burgard, Rupp, this issue] at the age of 8.5 years are in favour of the German recommendation.

The longitudinal IQ profiles showed a gradual and significant decrease over time, and the interaction of cluster by time indicated a steeper decrease for the cluster poor from age 4 to age 5. The decrease from age 5 to age 9 in the cluster poor, though greater than in the clusters good and intermediate, was 4.63 IQ points and very similar to the decrease found in healthy controls. Since the data of the healthy children investigated in the LOGIC study [29] showed the same structure as those of the patients, it can be concluded that the apparent gradual deterioration of the IQ was an artifact due to different test norms. The mean differences of 7 IQ points between the CMMS at the age of 4 and the WPPSI at the age of 5 and of 3.5 points between WPPSI and WISC-R at the age of 9 years cannot be attributed to obsolete norms [7, 9, 24] since all three tests had been standardized between 1972 and 1975.

Without the data of the healthy children the hypothesis of a specific impairment intelligence would have been accepted since performance IQs in both tests were smaller than verbal IQs. However, the healthy children showed the same pattern as in patients, indicating that subtest differences have to be regarded as normal, and that PKU patients did not show particularly reduced cognitive problem solving capacities.

Phe levels of the cluster poor were beyond any recommendation and the IQ profile showed a steeper decrease than all three other subsamples from age 4 to age 5 in the range of 12 IQ points, indicating an influence of Phe levels higher than the recommendations during the preschool years, but not later on. The mean differences between IQ at 5 years and IQ at 9 years were almost identical for healthy children (–4 points) and patients of the cluster poor (–4.63 points). Mean subscale differences were parallel for patients as well as healthy children. In particular this finding can be regarded as an argument to favour the hypothesis of a general depression of IQ scores due to elevated Phe levels; a result possibly related to neuropsychological impairments of reduced attentional capabilities and slower mental speed [22].

Our results support the recommendation of a strict Phe control during the first decade of life, but do not allow to decide whether the more strict German or the more liberal British recommendation for the school years are more rational. It was demonstrated that the interpretation of lon-

gitudinal data of children with PKU can circumvent serious pitfalls when comparison data from healthy subjects are included in the analysis. Within the empirical range of compliance observed in this study an influence of blood Phe level on IQ development after the age of 6 years could not be demonstrated. The mean IQ differences between all three cluster groups on the one side and the healthy comparison group on the other were significant but the differences between performance IQ and verbal IQ could not be interpreted with reference to the hypothesis of neurotransmitter imbalance resulting in domain specific deficits of intellectual functioning like problems in arithmetics[1], language acquisition and problem solving [16] nor executive functions [6, 16, 30]. Rather it had to be concluded that the elevated Phe levels, at least in the range observed, resulted in a generalized moderate reduction of intelligence.

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Appendix

German collaborative study centres

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