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Long-term development of intelligence (IQ) and EEG in 34 children with phenylketonuria treated early

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Abstract. In 34 children with phenylketonuria (PKU) treated early the prognostic value of the age on institution of the diet (within the first 3 months of life) and of the quality of dietary treatment was determined in two different ways: 1) following intelligence closely (IQ) and (2) evaluating the EEG development up to their 12th ($n = 34$) and 15th ($n = 18$) years of life as appropriate. In general, IQ scores were found to be normal from the 4th–15th years of life. In our group of patients there was no effect on the IQ of the timing of diet onset. Children with "strict" dietary control showed a significantly higher IQ than those with "loose" control. One hundred and fifty-four EEGs (10/20 system, awake with eyes closed) were recorded at intervals of 2 years and conventionally evaluated. The development of alpha-activity was found to be normal. Beta-activity was enhanced. Abnormal EEG findings like general slowing and generalized paroxysmal activity (GPA) with or without spikes were more frequent in children with PKU than in controls, with the exception of focal abnormalities. EEG abnormalities increased with advancing age independently of IQ development and showed no relation to either the age at the onset nor the quality of dietary treatment.

Key words: CNS development – Dietary treatment – EEG – IQ – Phenylketonuria

Introduction

Phenylketonuria (PKU) is an autosomal recessive disorder of phenylalanine (PHE) metabolism. Without treatment it leads to severe impairment of psychomotor development, to seizures, and to abnormal EEG findings [24, 26]. Treatment with a PHE-restricted diet [2] has proven its effectiveness. Nearly or totally normal intellectual development is amply documented [1, 12, 14, 30, 33, 36]. For this outcome two factors are considered to be of prime importance: The patient's age at the onset of diet regulation and the long-term control of dietary treatment [1, 13, 31, 36]. How strictly the diet should be followed and at what age it can be relaxed are questions still under discussion [5, 13, 18, 27–29, 34].

Concerning the EEG of PKU patients treated early, conflicting results have been reported showing a normal or elevated frequency of EEG abnormalities [3, 11, 20, 22, 24, 25]. The prognostic value of these changes in patients without seizures or impairment of their psychomotor development remains obscure. The same holds true for the significance of EEG changes when PHE blood levels rise under a PHE-restricted diet, under relaxation of this diet or after termination [5, 32].

In a retrospective study of 34 PKU patients treated early in our hospital, we examined their cerebral development in respect to IQ and EEG changes.

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Abbreviations: PKU = phenylketonuria; PHE = phenylalanine; GPA = generalized paroxysmal activity; IDC = index of dietary control

Patients and methods

Patients

For the study we accepted 34 (17 m; 17 f) children with "classical" PKU [4] who satisfied the following criteria: (1) PHE level of > 20 mg/dl on a normal diet, (2) no defect in the co-factor system, (3) onset of dietary treatment during the first 3 months of life, (4) no indication of any other factors influencing the psychomotor development or the EEG, such as perinatal hypoxia, traumatic lesions of the CNS etc. At the time when the data were collected all 34 children were at or over 12 years of age. Eighteen of these had reached their 14th of 15th year.

Diet inception and PHE blood levels

We defined as diet inception that day after birth on which after starting the diet the PHE level for the first time did not exceed 10 mg/dl. On the basis of this criterion the total sample was divided into two subgroups of equal size, each containing 17 children. One consisted of children with "early" diet inception, the other of those with "late" diet inception.

To determine the PHE levels, Guthrie tests were performed weekly or twice monthly up to the 2nd year, afterwards generally on a monthly basis. In addition, quantitative serum column chromatography was performed at the beginning and thereafter every 2–3 months. For each 6-month period we computed the median PHE value for every patient. The overall mean for the total duration of the diet up to the 12th year was derived from these 6-month median values. It served as an index of dietary control (IDC) for every child and was used for evaluating the long-term quality of dietary treatment.

Based on the IDC values the total sample of 34 patients was divided into two further subgroups of 17 cases each. One consisted of patients with "strict" dietary control, the other of those with "loose" dietary control.

Intelligence tests

Every child's full scale IQ score was recorded using the Binet-Kramer and Hawik (German version of WISC) tests. Beginning in their 4th year we tested the children usually once a year. The consistency of the test monitor was ensured. For five age ranges, each comprising 2 years (4th/5th, 6th/7th,

8th/9th, 11th/12th, 14th/15th year of life), the test results – separated according to the test methods used – were combined by computing the mean. For the age range 14th/15th year test results were available for only 13 children.

EEG

For each of the 2-year segments as defined above, two neurologists evaluated independently one resting EEG (10/20 system) from every child, a total of 154 EEGs. For the age range 14th/15th year we had EEG recordings from only 18 children. In the case of discrepancies, the EEG was evaluated a third time during a neurological staff meeting. For documentation a standardized evaluation sheet was used.

The evaluated EEGs were categorized into one of three groups: (1) normal EEG for the age group; (2) borderline EEG with slight deviations, such as irregularly dispersed sharp elements, questionable focal abnormalities, or an extreme degree of reaction to hyperventilation; (3) abnormal EEG with changes such as general slowing, focal abnormalities, generalized paroxysmal activity (GPA) without spikes (monomorphous theta and delta waves, paroxysmal bursts of occipital 3–4 cps. rhythms, paroxysmal dysrhythmia) and/or with spikes (spikes, sharp waves, spike and slow wave complexes $<2.5->3.5$ cps., polyspike and slow wave complexes, the combination of irregular and slow waves and spikes).

As a control group we used a sample of 172 healthy children, aged 3–16 years, whose parents were also healthy. For every child three EEGs were recorded in 1–5-year intervals. We obtained a fourth EEG recording for a number of these children ($n = 52$). In the control group, 516 EEG records were evaluated.

Calculations and statistical analysis were performed at the Computer Centre of the University of Heidelberg. For statistical decisions the chi-square test, Student's *t*-test and rank correlation analysis (Spearman) were used.

Results

Intellectual development

On diet inception, the children's mean age was 40.7 (14–90) days (Fig. 1).

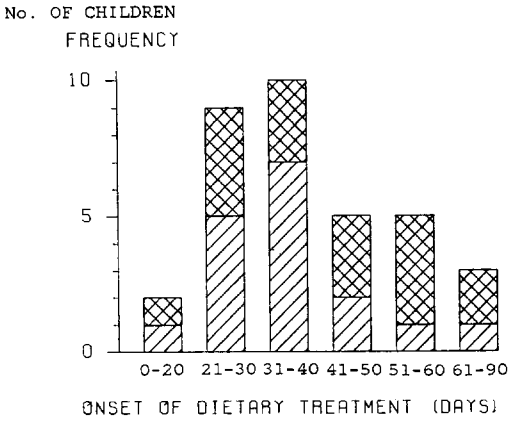

Fig. 1. Age at onset of dietary treatment within the first 3 months of life in 34 PKU patients (17 male ▨; 17 female ▩). PKU = phenylketonuria

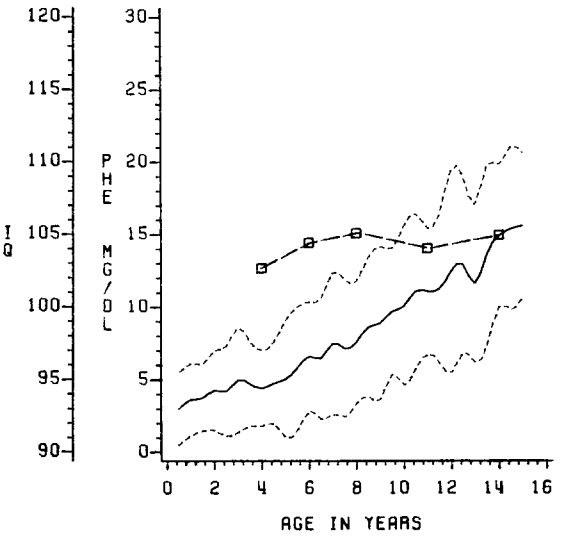

Fig. 2. Blood levels of PHE (——) and their standard deviation (+/− SD ----) during treatment and IQ (--□--) for five age ranges between the 4th and 15th year of life in 34 early treated PKU patients. PHE = phenylalanine

For the total sample, the mean index of dietary control was 6.9 (3.4–11.8) mg/dl PHE.

The PHE median values increased in the total sample with the patients' advancing age: The PHE levels rose continuously from the time of diet inception up to age 15. They varied greatly from one individual case to another (Fig. 2).

From their 4th to their 12th or 15th year, our PKU patients obtained a full scale IQ score appropriate for their age group and comparable to that of the normal population (Table 1). There was no significant sex difference.

Intellectual development and dietary inception

In the subgroups "early" diet inception (mean age: 27.5 (14–36) days) and "late" diet inception (mean age: 54 (37–90) days) boys and girls were equally distributed. They showed a comparable index of dietary control (IDC 6.2 mg/dl and 7.4 mg/dl PHE respectively, see below). At no age range was there a statistically significant difference between the mean IQ of the subgroup with "early" diet inception and that with "late" diet inception. The mean IQ of both subgroups corresponded to the result of the total sample (Table 1). A rank correlation analysis (Spearman) between the age at diet inception and the IQ obtained for the five age ranges (diet inception × IQ) showed no significant correlation coefficients for any age range.

Intellectual development and quality of the dietary control

The subgroup with "strict" dietary control had a mean IDC of 4.7 (3.4–6.2) mg/dl PHE, the other with "loose" dietary control of 9.0 (6.3–11.8) mg/dl PHE. Again boys and girls were equally distributed in these groups. With approximately equal values during the first 6 months, PHE levels definitely rose at a sharper angle in the group with "loose" dietary control than in the "strict" dietary control group (Fig. 3).

The children with "strict" dietary control reached significantly higher IQ scores when compared to those with "loose" dietary control (Table 1). The rank correlation analysis

Table 1. IQ of 34 PKU patients treated early

Age in years	IQ of 34 PKU patients				
	N	IQ	SD	min.	max.
4th/ 5th	34	102.6	10.3	80	119
6th/ 7th	34	104.4	13.3	77	145
8th/ 9th	34	105.1	16.5	72	137
11th/12th	34	104.0	15.5	61	134
14th/15th	13	104.9	10.6	86	123
IQ of 17 PKU patients: 'Early' diet inception (14–36 days)					
4th/ 5th	17	101.8	11.2	80	119
6th/ 7th	17	102.3	12.3	77	121
8th/ 9th	17	106.2	19.2	72	137
11th/12th	17	105.6	18.5	61	134
14th/15th	5	104.8	6.3	99	115
IQ of 17 PKU patients: 'Late' diet inception (37–90 days)					
4th/ 5th	17	103.5	9.5	86	119
6th/ 7th	17	106.5	14.3	83	145
8th/ 9th	17	103.9	13.8	79	136
11th/12th	17	102.4	12.1	77	123
14th/15th	8	105.0	13.0	86	123
IQ of 17 PKU patients: 'Low' PHE (IDC 4.7 mg/dl)					
4th/ 5th	17	106.9	8.9	90	119
6th/ 7th	17	108.2	13.2	90	145
8th/ 9th	17	114.1	15.9	79	137
11th/12th	17	112.1	12.1	82	134
14th/15th	6	112.0	10.1	99	123
IQ of 17 PKU patients: 'Elevated' PHE (IDC 9.0 mg/dl)					
4th/ 5th	17	98.4	10.0	80	113
6th/ 7th	17	100.5	12.5	77	121
8th/ 9th	17	96.1	11.5	72	116
11th/12th	17	95.9	14.4	61	114
14th/15th	7	98.9	6.8	86	106

See text. PKU = phenylketonuria; PHE = phenylalanine; IDC = index of dietry control

(Spearman) between the quality of the dietary control and the IQ obtained at each age range showed significant correlation coefficients for all age ranges (Table 2).

EEG development

Background activity. The patients developed an alpha background activity appropriate for their age in terms of amount and frequency when compared to the healthy control group: In the range 4th/5th year, the majority (82%) showed little (<25% of the recording time) alpha-activity. Beginning with their 8th/9th year, all had a fairly (56%; 25%–75% of the recording time) or well (44%; >75% of the recording time) established alpha-activity. The same holds true for the frequency of alpha-activity, which increased with advancing age as appropriate for the different age levels. During the 8th/9th year an alpha-frequency higher than 10/s was recorded in 30%, in the 14th/15th year it increased to 61% of the EEGs.

Beta-activity was registered in 98 (64%) of the 154 EEGs, mostly (81 EEGs) from frontal leads. It was found in the EEGs of all age ranges. From the 4th to the 7th year, beta-activity (>25% of the recording time) occurred somewhat more frequently than from the 8th to the 15th year (38% versus 20% of the EEGs).

Sixty-five percent of all EEG recordings (101 EEGs) showed disturbances of the background activity, mainly slow and/or sharp transients (localized occipitally on both sides), irregular sharp elements, and groups of theta/delta rhythms. These disturbances occurred more often with advancing age. They increased from 44% of the EEGs during the 4th/5th year to 76% during the 11th/12th and to 77% in the 14th/15th year. These irregular disturbances of the background activity were not distributed in a specific pattern according to age.

Sixty-six (43%) of the 154 EEGs were classified as exhibiting signs of a general slowing, which was for the most part low grade. In 47 of those 66 EEGs (31% of the total) the general slowing occurred in combination with focal abnormalities and/or GPA. The percentage of EEGs with general slowing increased with advancing age from 9% during the 4th/5th to 83% during the 14th/15th year.

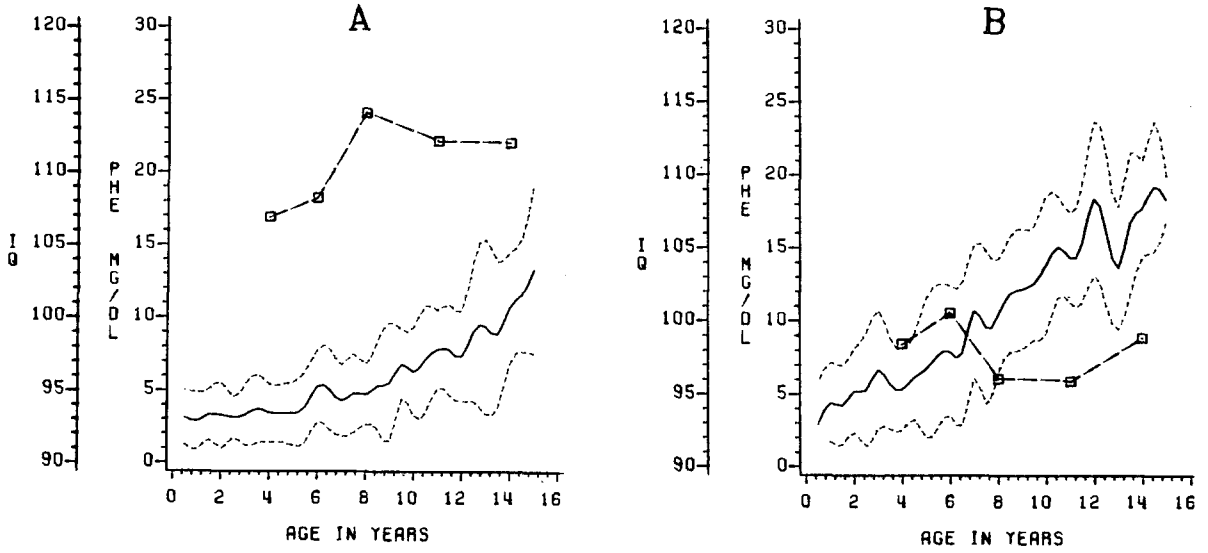

Fig. 3. Blood levels of PHE (——) and their standard deviation (+/− SD ----) during treatment and IQ (--□--) for five age ranges between the 4th and 15th year of life in two subgroups (*A/B*) of 17 PKU patients treated early each; subgroup A consists of children with 'strict' dietary control and subgroup B of children with 'poor' dietary control

Table 2. Rank correlation coefficients (Spearman) of (1) diet inception × IQ; (2) blood level PHE × IQ in 34 PKU patients treated early

Age in years	*N*	Correlation coefficient	significance
1. Diet inception (days) × IQ			
4th/ 5th	34	−0.04	n.s.
6th/ 7th	34	0.12	n.s.
8th/ 9th	34	−0.17	n.s.
11th/12th	34	−0.26	n.s.
14th/15th	13	−0.29	n.s.
2. Blood level PHE (up to IQ testing) × IQ			
4th/ 5th	34	−0.60	$P<0.0005$
6th/ 7th	34	−0.50	$P<0.005$
8th/ 9th	34	−0.63	$P<0.0001$
11th/12th	34	−0.61	$P<0.0001$
14th/15th	13	−0.73	$P<0.005$

For abbreviations see Table 1

Table 3. Frequency of GPA in the EEGs of 34 PKU patients and 172 healthy controls (resting EEG without provocation methods)

	PKU patients (154 EEGs)	Healthy controls (512 EEGs)
GPA	38%	24%
GPA without spikes (type 1)	17%	11%
GPA with spikes (type 2)	10%	13%
Type 1 + type 2	11%	–
Age distribution of GPA		
Age in years		
4th/ 5th	29%	21%
6th/ 7th	38%	23%
8th/ 9th	30%	30%
11th/12th	41%	28%
14th/15th	67%	24%
(Frequency of GPA related to no of EEGs)		

GPA = generalized paroxysmal activity. For other abbreviations see Table 1

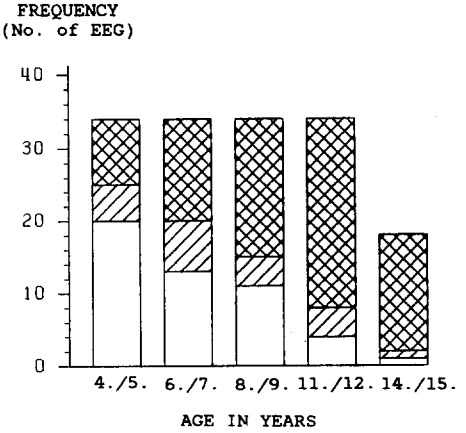

Fig. 4. EEG findings of 34 PKU patients treated early from 4th/5th to 14th/15th year of life, categorized as either normal (□) or borderline (▨) or abnormal (▩)

Table 4. EEG findings 4th–12th year of PKU patients with 'high' and 'low' IQ at 12 years of age

	24 Children IQ > 100 (96 EEGs)	10 Children IQ < 100 (40 EEGs)
Normal EEG	35 (36%)	13 (32%)
Borderline EEG	15 (16%)	4 (10%)
GPA with spikes	14 (15%)	6 (15%)
GPA with spikes (residual)	5 (5%)	3 (7%)
GPA with spikes (on provocation)	4 (4%)	5 (12%)
Abnormal EEG (other abnormalities)	23 (24%)	8 (20%)
(Frequency of EEG findings related to n of EEGs)		

For abbreviations see Tables 1, 3

Focal abnormalities. Focal abnormalities were observed in 15 EEG recordings (10%) of the patients compared to 40 EEGs (8%) of the control group. Focal sharp waves (four EEGs) and sharp slow waves (five EEGs) were mostly seen in the PKU patients. Focal abnormalities were equally distributed at all ages up to 15 years.

Generalized paroxysmal activity. In the resting EEGs (without provocation methods) GPA without and/or with spikes was seen in 38% of the EEGs of PKU patients and in 24% of the control group (Table 3). With advancing age, we registered a steady increase of GPA in the PKU patients. In contrast, GPA occurred in the control group most frequently during the 8th/9th year and decreased afterwards (Table 3).

Among the PKU patients GPA without spikes consisted mostly of bursts of occipital 3–4 cps. rhythms. They were found in 20 (13%) EEGs. In the case of GPA with spikes, the combination of irregular slow waves and spikes was registered most frequently, namely in 21 (14%) EEGs. The paroxysms were of short duration, mostly less than 2 s (60% of the EEGs with GPA).

Hyperventilation was performed in 123 EEG recordings and led to a provocation of GPA without spikes in 4 EEGs. In 11 EEG recordings GPA with spikes was provoked. Photic stimulation (performed in 66 EEG recordings) resulted in a provocation of GPA with spikes in five cases.

Clinical categorization of the EEG. Abnormal EEGs increased steadily with advancing age up to the 14th/15th year of life (Fig. 4).

There was no relationship between abnormal EEGs from the 3rd/4th–11th/12th years of life and the IQ score obtained during the 11th/12th year. At that age ten children with an IQ of > 100 did not differ from the 24 children with an IQ of < 100 with regard to the frequency of normal, borderline, or abnormal (especially GPA with spikes) EEGs (Table 4). There was also no relationship between abnormal EEGs and an increase or decrease of IQs from one age range to the next.

EEG development in relation to diet inception and quality of dietary control. A difference in the age-related development of the alpha background activity could not be established between the subgroups. The occurrence of abnormal EEG recordings during the 4th to the 15th year correlated neither with the age at diet inception nor with the quality of the dietary treatment. The increase with advancing age was the same for all subgroups and corresponded to the result of the total

sample. Similarly, significant differences with regard to specific EEG findings such as general slowing, focal abnormalities or GPA did not exist.

Discussion

Intellectual development

Between the 4th and the 15th year, the group means of the IQs were well within the normal range. Thus we are able to confirm previous reports [8, 12, 36] stating that children with PKU treated early have a normal intellectual development. In contrast to Knoll et al. [17] a significant decrease in IQ scores from the 8th year on was not noticed. Earlier studies [1, 7, 15, 16] and also the recent US Collaborative Study [13] report, despite an early onset of dietary treatment, slightly lower IQs of the PKU children when compared to their healthy siblings or their parents.

Since we only registered full scale IQ scores, statements about partial deficiencies – as other researchers have been able to state – are impossible. Koch et al. [18], for example, demonstrated that PKU children treated early suffer from deficits in visual skills (using the Bender-Gestalt Visual-Motor test). Pennington et al. [23] found neuropsychological deficits in conceptual and visuospatial skills among six PKU children treated early at 9 years of age. In 50% of PKU children treated early with normal IQ (Stanford-Binet), Melnick et al. [21] found that linguistic skills develop at a slower rate.

In our study the children's mean IQ in the two subgroups with "early" and "late" diet inception did not differ significantly at any age range. Similary, Steinhausen and Börner [30] did not find any differences in the intellectual development, whether the treatment was started in the 1st or 2nd month of life. In our sample the number of children with diet inception during the 3rd month, with three cases, is very low (Fig. 1). Therefore our results concerning the 3rd month of life should be weighed carefully. On the basis of the prospective US Collaborative Study [35, 36] dietary treatment beginning as early as possible has to be recommended. At 6 years of age their PKU patients whose diet was regulated within 30 days of birth obtained a significantly higher mean IQ than those with a later onset of treatment. But when tested again at 8 and 10 years the age (in days) at which treatment was started could not be confirmed as a significant predictor of IQ (WISC) [13].

In our sample children with a "strict" long-term dietary treatment obtained a significantly higher IQ than those with "loose" dietary control. So likewise did the children of the US Collaborative Study [8, 36]. We found this positive effect of "strict" treatment up to early adolescence. The necessity for longer treatment than usual should be discussed again, also taking into account the results reported by Holtzman et al. [13] for the US Collaborative Study. Performing multiple regression analysis the age at which the subjects' PHE blood level (during the 6-month period before the IQ test) first exceeded and remained above 15 mg/dl was the most significant indicator of the child's IQ at the age of 8 and 10 years.

We found an increase of PHE levels with the patients' advancing age in the whole sample and in our subgroups, which is also reported by Koepp et al. [19]. Yet, it is striking that the IQ difference between the two subgroups was manifested already during the 4th/5th and 6th/7th years, whereas the PHE levels differed more markedly at later ages (Fig. 3). An explanation could be that the children with "loose" dietary control already at an early age exceeded a "critical" limit of PHE blood levels. But the authors' hypothesis is that other factors interact in the children's intellectual development. "Competent" parents who succeed in making their child adhere strictly to the diet might on the whole be capable of creating a beneficial environment for their child's development. Therefore, the better intellectual development of the children with "strict" dietary control – already present at their 4th/5th year of life – might be due to the lower PHE levels as well as to a nurturing home environment and/or to a higher IQ that was genetically transmitted. Further investigations should be made to differentiate among these factors.

EEG

Children with PKU treated early show on the whole a normal development of the alpha background activity. Our ranges to classify the amount of alpha-activity ($<25\%/25\%-75\%/>75\%$) are, however, fairly large. For a more detailed study Computer Spectral Analysis should be performed.

The fairly frequent occurrence of beta-activity at all age ranges was striking but probably has no specific clinical importance. Its particular patho-physiological significance is still uncertain [10].

Concerning the EEG development, the most important result is the fact that abnormal EEG recordings increased steadily with advancing age. This increase affects all non-specific and specific EEG changes with the exception of focal abnormalities. It is noteworthy that the occurrence of generalized epileptiform activity is not coupled with clinically manifest seizures. Hypsarrhythmia, which is often observed in children with diet inception after the 3rd month of life – usually occurring in combination with clinically manifest seizures [20] –, was not registered in our total sample. It seems that hypsarrhythmia occurs after the 3rd month in non-treated PKU patients, whereas other types of epileptiform activity, especially the combination of irregular slow waves and spikes, may occur also in patients treated early.

There are several reports [11, 24, 25] stating that PKU leads to an age-related increase in abnormal EEG findings despite early onset of diet and strict dietary control. Gross et al. [11] found that with advancing age the EEGs showed an increase in general slowing, beta-activity, and GPA with spikes in a group of PKU children treated early. In that respect these and our results deviate from those of the Collaborative Study: Blascovisc et al. [3] registered the same EEG changes – both with regard to their quantity and their quality – in patients aged 1 and 6 years as compared to the normal population. At or immediately after birth abnormal EEGs (19 out of 167) had become normal by 1 and 6 years of age in all but two patients. Comparing our results to others one has to remember that our children were subjected to EEG examinations much more frequently and over a considerably longer period of time.

There was no correlation between abnormal EEGs, especially between the occurrence of GPA, and the children's mental development in our sample. This lack of correlation has been observed in other studies [11, 24, 25], though there are also conflicting results [22]. The missing correlation may indicate a disturbance of CNS function caused by the original disease that is not picked up in the full scale IQ score. However, the full significance of abnormal EEGs in PKU children treated early so far remains obscure. Results from advanced

neuropsychological testing may provide a link between EEG abnormalities and slight deficits in psychomotor skills.

In our series, patients with "early" diet inception did not differ from the "later" treated children with regard to the development of background activity or the frequency of abnormal EEGs.

Similarly, no connection between the quality of the dietary control and the occurrence of abnormal EEG patterns could be established. Rolle-Daya et al. [25] came to the same conclusions in a group of 48 children whose diet was started during their first 4 weeks of life. In contrast to our study, however, they found normal EEG recordings in 73% of these patients, abnormalities of the background activity only in 23%, and GPA in 4% of the EEGs. An important difference between their study and ours lies in the fact that they performed only one or, at the most, two EEG recordings per child. Furthermore an age distribution is not documented, which renders a comparison difficult.

A study of the EEG after loading PKU children with phenylalanine suggests that the actual PHE level at the time of the EEG recording is only a weak predictor of the EEG [6]. In addition, elevated actual PHE levels usually lead only to reversible changes in the frequency spectrum of the dominant background activity [9]. In our sample however, the PHE level on the day of the EEG recording deviated only rarely from the overall trend as registered in the median for that particular 6-month period. Therefore, in all likelihood, the EEG changes we describe in our study are not caused by the actual PHE level on the particular day of the EEG recording.

The changes in background activity under abruptly elevated PHE levels that can be noticed only in computerized frequency analysis are thought to represent a "toxic" effect. In contrast paroxysms as seen in the EEGs of our study might be the result of a more prolonged and permanent effect of elevated PHE levels on the developing brain. This long-term disturbance of CNS function is in accordance with our results not of a focal but of a diffuse character. Conventional EEG recordings show an interesting additional aspect of the disease but seem to be of little value for monitoring PKU patients, for example when deciding to terminate the dietary treatment [32].

Conclusions

Reviewing our results concerning the intellectual development of children with PKU, a strict long-term dietary control is recommended. Already at an early age it is mandatory to detect steeply increasing PHE levels. In this case improved services to help the families in dealing with the sick child and in applying the diet properly should accompany the usual clinical routine in monitoring PKU patients. In addition, testing for partial deficits in cognitive skills seems to be necessary also for children with a normal full scale IQ.

Concerning our EEG results, the significance of abnormal EEG findings for decision in clinical routine and for the long-term prognosis of PKU children treated early remains obscure. Further investigations to link IQ and EEG data in addition to advanced neuropsychological methods should include neurophysiological ones, e.g. computerized EEG techniques like frequency analysis and evoked potentials.

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YOU MUST always be students, learning and unlearning till your life's end, and if, gentlemen, you are not prepared to follow your profession in this spirit, I implore you to leave its ranks and betake yourself to some third-class trade.

Lister