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Neurocognitive functioning in adults with phenylketonuria: Report of a 10-year follow-up

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A B S T R A C T

Background: The long-term prognosis of early treated phenylketonuria (PKU) is still under discussion. Aim of this controlled long-term study was to assess the neurological and neuropsychological outcome in adult patients with early-treated PKU.
Methods: We investigated 35 patients with early-treated classical PKU aged 29 to 51 years (mean age 41 years) and 18 healthy controls matched for age and socioeconomic status. Patients and controls were assessed for their intelligence quotient (IQ), attention and information-processing abilities. Magnetic resonance imaging (MRI) of the brain was performed in all patients. Neuropsychological assessments and MRI were repeated at a five-year and a ten-year follow-up.
Results: In the entire interval IQ, information processing and attention of patients and controls remained constant. At both follow-up assessment times the IQ scores were significantly lower in patients compared to controls. Older adult patients (> 42 years) showed poorer information processing and attention at both assessment times compared to young adult patients (< 42 years) and controls. IQ, information processing and attention showed no correlation to imaging results. IQ, however, was significantly correlated to blood phenylalanine (Phe) levels in patients´ childhood and adolescence, and Phe levels had been higher in the adolescent years of older adult patients.
Conclusions: Cognitive performance in adult patients with early-treated PKU does not seem to deteriorate in a ten-year interval. Neuropsychological assessment in adults with PKU revealed neurocognitive impairment particularly in older adult patients. This seems to refer to an early relaxation of diet that was recommended when the older patients were adolescents. Results indicate a benefit of dietary control during adolescence in PKU.

1. Introduction

Phenylketonuria (PKU) is a rare metabolic disorder with an estimated prevalence of 1:10.000. Inheritance is autosomal recessive caused by mutations in the phenylalanine hydroxylase (PAH) gene. Due to absence or deficiency of PAH, phenylalanine (Phe) cannot be converted into tyrosine, resulting in a toxic accumulation of Phe an a tyrosine deficiency. We define classical PKU as natural blood Phe levels under free nutrition > 1.2 mmol/L. Phe levels above 1.2 mmol/L are leading to concomitantly elevated brain Phe levels. Untreated PKU, thus, leads to severe mental and psychomotor retardation [1].

If a diet is initiated shortly after birth that is strictly Phe-reduced and supplemented with a Phe-free amino acid mixture, mental and psychomotor retardation can be prevented. However, in spite of strict and early dietary treatment, outcome in young patients with PKU is suboptimal [2]. Patients show mild reduction of intelligence, neuropsychological deficits, and cerebral white matter abnormalities [3,4]. Studies described reduced attention abilities, slow information processing and motor reaction time as well as changes in the frequency distribution of brain electrical activity [5]. Single adult patients developed severe neurological deterioration years after ending dietary treatment. Some improvement was noticed after reintroducing a Phe-restricted diet [6]. Up to now, studies in adolescence and adulthood are rare, presenting cross-sectional results suggesting that manifest cognitive impairment is found in a minority of patients. Childhood Phe levels, adult Phe levels or current Phe levels are predicting adult cognitive outcome depending on the cognitive tasks selected [7,8]. In a retrospective study in young adults with PKU IQ over the second decade of life remained stable in about half of the patients while the rest experienced a gain or loss in IQ scores independent to their quality of metabolic control [9].

National recommendations for treatment of adolescents and adults are diverging as far as the target levels of blood Phe in teen age and adulthood are concerned [10].

Abbreviations: d2, Sustained Attention Test; HPA, Hyperphenylalaninemia; HPLC, high-performance liquid chromatography; IQ, intelligence quotient; MRI, magnetic resonance imaging; Phe, phenylalanine; PKU, phenylketonuria; SD, standard deviation; WAIS III, Wechsler Adult Intelligence Scale; ZVT, Zahlen-Verbindungs-Test

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Aim of our study was to examine the neurological status of adult early-treated patients with classical PKU in a long-term control-group design, and to assess cognitive, information-processing and attention abilities in order to detect possible consequences of long-term elevated blood Phe Ievels in adulthood. We already presented study data of a five-year follow-up that showed not deterioration in patients´ cognitive abilities [11].

2. Methods

We examined 35 early-treated adult patients (22 women, 13 men, mean 41.7 years, SD 5.9 years, range 29 to 51 years) with classical PKU (Phe levels above 1.2 mmol/L) who met the following criteria: start of diet within the first 10 weeks of life (mean: 7.6 weeks., SD: 2.4 weeks), ten blood-Phe-measurements per year up to the age of 10 years at a minimum, eight blood-Phe-measurements per year between the 11th and 20th year of life at a minimum, and six blood-Phe-measurements per year at a minimum after the 20th year of life. Healthy controls ($N = 18$, 7 women, 11 men) were matched for age (mean 44.2 years, SD 11.6 years, range 30 to 54 years) and socioeconomic status. Regarding the educational qualification and current occupation of the adults, patients and controls were classified according to the following categories of socioeconomic status: lower (1 patients, 1 control), lower to middle (25 patients, 12 controls), and middle (6 patients, 5 controls).

Blood levels of Phe were determined by high-performance liquid chromatography (HPLC) methods following standard procedures. Lifelong metabolic control was estimated by calculating the mean of all yearly medians of Phe levels since start of treatment. In addition, the concurrent Phe levels at the time of investigation were determined. Patients were seen for regular follow-up appointments at the Center of pediatrics at University Hospital Muenster. Informed written consent was obtained in all cases (patients and controls) after the nature and possible consequences of the study were fully explained. Consent to the study protocol was given by the local ethic committee.

2.1. Assessment program

2.1.1. Magnetic resonance imaging

Magnetic resonance Images studies were acquired on a 1.5-Tesla clinical imaging system (Gyroscan Intera, Philips, Best, The Netherlands). Axial PD- and T_2-weighted spin-echo images as well as coronal and sagittal T_1—weighted spin-echo images were acquired. The MRI scans were evaluated by a radiologist (JF) not involved in the clinical and psychological examination. In particular, they were graded according to severity and extent of white matter changes [4]. A normal scan was graded “0”, grades “1” to “2” represented increasing white-matter involvement. Scores “0” to “2” were given for each of the following anatomical regions: frontal, parietal, occipital, temporal, cerebellum and brainstem.

2.1.2. Neuropsychological performance

Patients and controls were assessed for intelligence quotient (IQ) using the Wechsler Adult Intelligence Scale (WAIS-IV). Verbal, performance, and full-scale scores were obtained. The widely used Wechsler test has excellent psychometric properties [12].

Information processing was measured by the trail-making test (“Zahlen-Verbindungs-Test”, ZVT). Trail-making tests are used widely in the screening of psychomotor function. They require visual-motor tracking and basic sequencing skills. Trail changes require that the subjects shift between rehearsed sequences, thus providing a measure of sequencing skills [13]. The ZVT consists of four subtests, in which different trails are to be made. The mean time needed to make the trails is calculated as a score of information processing speed.

Sustained attention was assessed by the Test d-2, a paper and pencil test that measures speed and accuracy in differentiating similar visual stimuli [14]. Results are expressed in the following scores: N (number of items completed) and M (Mistakes = number of mistakes, i.e. missed target items plus ommissions). N is described as a measure of basic cognitive working speed, and M is described as an index of selection abilities.

Data analysis was based on *t*-tests for independent samples and on Pearson correlations. The significance tests were of an explorative nature; the level of significance was set up at $p < 0.05$. Statistical analyses were carried out using PASW 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Patients reached a mean IQ that was within the normal range (100 ± 15) but below the IQ of the healthy controls (though not significant). As a group, patients did not need significantly more time to run through the trail making test (ZVT) and to complete the attention task (Test d2). Within the ten year interval, the performance of patients and controls remained constant (Table 1).

Younger and older adult patients (age < 42 years vs. age > 42 years, according to the median of patient age) did not significantly differ in their IQ-results. Younger patients and older controls kept with the pace of younger controls. Older patients only showed a distinct slowing in their information processing without making more mistakes. Within the ten-year interval, the performance of both patient groups remained constant (Table 2).

In virtually all patients (96%) MRI showed abnormalities of white matter. Within the ten year interval, the imaging results of patients showed an increase (Table 3). Younger and older adult patients did not significantly differ in the degree of white matter abnormalities (data not shown).

There were no significant correlations of MRI abnormalities with IQ in patients (data not shown). However, IQ in adult patients with PKU was significantly correlated to blood Phe levels in childhood and

Table 1
Results of the Full Scale IQ (WAIS), the trail making test (ZVT; Sec = seconds needed to complete trail) and the test d2 (concentration performance) in adults with PKU and healthy controls.

Scale	PKU (N = 35)	Control (N = 18)	p[1]
	Mean ± SD	Mean ± SD	
Full scale (WAIS III) at first examination	92.5 ± 20,0	100,9 ± 14.6	n.s.
Full scale (WAIS III) at five-year follow-up	88,5 ± 17.3	95.7 ± 15.5	n.s.
Full scale (WAIS IV) at ten-year follow-up	94.5 ± 17.9	101.4 ± 16.2	n.s.
Sec (ZVT) at first examination	81.8 ± 52.8	70.2 ± 16.2	n.s.
Sec (ZVT) at five-year follow-up	81.6 ± 58.0	69.3 ± 13.0	n.s.
Sec (ZVT) at ten-year follow-up	72.2 ± 34.4	68.7 ± 17.9	n.s.
Concentration performance (d2) at first examination	160.0 ± 45.7	170.9 ± 40.7	n.s.
Concentration performance (d2) at five-year follow-up	157.9 ± 53.2	158.7 ± 25.3	n.s.
Concentration performance (d2) at ten-year follow-up	142.5 ± 42.3	143.5 ± 34.4	n.s.

[1] *t*-test; n.s. not significant.

Table 2
Results of the Full Scale IQ (WAIS), the trail making test (ZVT; Sec = seconds needed to complete trail) and the test d2 (concentration performance) in younger and older adult patients.

Scale	PKU < 42 ys (N = 17)	PKU > 42 ys (N = 18)	p[1]
	Mean ± SD	Mean ± SD	
Full scale (WAIS III) at first examination	96.8 ± 16,1	88.4 ± 22.9	n.s.
Full scale (WAIS III) at five-year follow-up	92,9 ± 11.1	85.2 ± 20.5	n.s.
Full scale (WAIS IV) at ten-year follow-up	102.9 ± 12.0	86.6 ± 19.3	*
Sec (ZVT) at first examination	63.5 ± 14.4	99.0 ± 68.8	n.s.
Sec (ZVT) at five-year follow-up	59.03 ± 12.8	98.1 ± 72.1	n.s.
Sec (ZVT) at ten-year follow-up	60.4 ± 13,0	84.0 ± 44.4	n.s.
Concentration performance (d2) at first examination	184.6 ± 39.5	136.9 ± 39.2	*
Concentration performance (d2) at five-year follow-up	191.9 ± 28.0	135.9 ± 54.5	*
Concentration performance (d2) at ten-year follow-up	163.3 ± 33.6	123.0 ± 41.1	*

[1] t-test; n.s. not significant.
* $p < 0.05$.

Table 3
MRI scores in adults with PKU.

	First examination	Five-year follow-up	Ten-year follow-up	p[1]
	Mean ± SD	Mean ± SD	Mean ± SD	
Total	3.1 ± 1.7	3.3 ± 2.4	5.0 ± 2.3	n.s.
Fontal lobe	0.54 ± 0.50	0.30 ± 0.5	0.73 ± 0.70	n.s.
Temporal lobe	0.17 ± 0.38	0.44 ± 0.59	0.64 ± 0.50	n.s.
Parietal	1.25 ± 0.74	1.13 ± 0.69	1.63 ± 0.58	n.s.
Occipital	1.08 ± 0.71	1.13 ± 0.81	1.63 ± 0.73	n.s.
Cerebellum	0 ± 0	0 ± 0	0 ± 0	n.s.
Brain stem	0 ± 0	0.26 ± 0.68	0.36 ± 0.69	n.s.

[1] t-test; n.s. not significant.

adolescence (Table 4).

4. Discussion

Well-controlled outcome studies are still missing in adult PKU. As the intellectual and physical development appeared to be quite normal under an early initiated Phe-restricted diet, neurological and neuropsychological evaluation in adulthood formerly was assumed not to be required. To date, neurological deterioration in several PKU adults years after ending the diet changed this assumption fundamentally. Studies on treated adult PKU patients revealed a high incidence of minor neurological signs indicating the possibility of a specific neurological syndrome in adult PKU patients [15].

In our study we investigated early-treated adult PKU patients with well-documented blood Phe levels since the time of birth. MRI showed typical white-matter abnormalities in 96% of our patients. This is in accordance with other studies [16]. Both our younger and older adult patients did not significantly differ in the degree of these abnormalities.

Table 4
Correlations of the Full Scale IQ (WAIS) in adults with blood Phe level in adolescence.

Blood Phe levels (median)	First examination	Five-year follow-up	Ten-year follow-up
	Full scale (WAIS III)	Full scale (WAIS III)	Full scale (WAIS IV)
	r	r	r
Age 0–10	−0.696**	−0.712**	−0.684**
Age 11–20	−0.661**	−0.622**	−0.672**
Age 21–30	−0.306	−0.373	−0.250
Age 31–40	−0.328	−0.407	−0.320

** $p < 0.01$.

Other studies, however, found low degrees in younger patients only [4].

Patients reached a mean IQ that was within the normal range but markedly below the IQ of the healthy controls. We found impaired information processing and attention only in the older group adult patients. Other neuropsychological studies of PKU revealed deficits primarily found in information processing speed and reduced attention abilities [17,18].

There were no significant correlations of MRI abnormalities with IQ, information processing, and attention in our patients. Global cognitive impairment and slow information processing, however, had been found to be related to white-matter pathology and age in 33 early-treated children but not in adult patients with PKU (as far as the IQ is concerned) [19,20]. Other studies found cognitive impairment in adult patients to be related to their dietary status [21,22]. Early termination of diet is known to cause a loss in intellectual functioning in children [23]. Koch et al. presumed that good dietary compliance after age 10 may contribute to a better cognitive status in PKU patients [24]. Van-Zutphen et al. showed a correlation of dietary compliance and executive functions of children and adolescents with PKU [25]. They suggest that a decrease of dietary compliance in adolescents may affect their executive functioning skills. However, a recent functional MRI study employing an adapted color-word matching Stroop task did not yield support for the assumption of distinctly altered functioning of brain networks crucially involved in executive functions [26].

Our data show a considerable slowing of information processing in older adult patients. In patients with slow information processing we did not find significantly more white-matter abnormalities. Thus, enduring MRI abnormalities in adult patients may not influence processing speed and attention, as there was no deceleration with age in the information processing in PKU patients. Poor performance in our older adult patients may be related to their early relaxation of diet (at age 10), whereas younger adult patients who had been off diet since early adulthood only, performed as well as healthy controls.

In summary, our results indicate that the neurocognitive outcome in adult patients with PKU is constant over a ten year timespan. Outcome, however, is better in those patients who continued their diet into early adulthood. Confirmed by a long-term follow up, our results suggest that recommendations of dietary control during adolescence require careful consideration. Adult PKU patients should continually be assessed to clarify whether neurological impairment will occur later in life and, thus, whether a Phe restricted diet is indicated in adulthood.

4.1. Limitations

Within the long follow up time, patients were increasingly hesitant to return to the pediatric University hospital for the assessments. To many of them, PKU was an issue they felt they had overcome in childhood. During the follow up period, 22 patients of the original

sample of 57 patients dropped out. The remaining sample of 35 patients is small and results may be rather tentative, thus. There is a lack of power in our study, and differences in test and/or subscale scores may be rated different in a larger sample which, however, is difficult to follow up for a long time.

Then again, drop outs may influence the results in the event that primarily those patients dropped out who had a lower socioeconomic status and a poorer outcome. A remaining sample should not comprise the `better off´ patients only. Fortunately, this was not the case.

At the five year-follow up, the 22 patients who eventually dropped out had a mean FSIQ of 90.7 compared to the FSIQ of the compliant 35 patients that was 90.4. Thus, those patients who were “lost to follow-up” show no deterioration within five years as well. Drop outs and compliant patients did not differ in their socioeconomic status, as well. Among the drop outs, untrained patients (“lower SES”) and patients with academic training (“middle”) were slightly more frequent.

A broader SD in patients than in controls in ZVT and sustained attention measurements emerges from the data reported. This is also confirmed when PKU subjects were sub-grouped as younger or older than 42 years: the oldest patients show a larger variability in ZVT and sustained attention scores. This is possibly reflecting individual factors (affecting the outcome) particularly in the patients older than 42 years.

Although the follow up time was characterized to be long, 10 years are certainly not sufficient to confirm good neurological and cognitive outcome in PKU in the long run. It is highly recommended to follow up neurological and cognitive development in adults with PKU for their entire life time.

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