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REVIEW

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Final intelligence in late treated patients with phenylketonuria

Abstract Despite neonatal screening programmes, there is still a number of patients with phenylketonuria who are not diagnosed and start treatment late. The question in this study was to evaluate which factors will contribute, other than the quality and duration of dietary treatment, to final outcome in late treated patients with phenylketonuria. We retrospectively analysed the data of 40 patients with phenylketonuria, of whom 2 patients at 35 and 24 years of age had a normal IQ despite never being treated. In 38 patients starting dietary treatment between 0.7 and 7 years of age, mean IQ/DQ at diagnosis was 52.7 (SD = 16) (mean age 2.5 years), final IQ (mean age 33.5 years) was 79.0 (SD = 16), the difference was highly significant ($P < 0.0001$). Important factors for the final intelligence in adult late treated patients with phenylketonuria were onset ($r = -0.46$, $P < 0.009$) and DQ/IQ ($r = 0.51$, $P < 0.002$) when dietary treatment was started. Thus, in late treated patients with phenylketonuria, in addition to the quality and duration of treatment, the outcome is mainly influenced by the age of starting treatment and also by the intellectual status of the patient. In one of the two patients with normal intelligence, nuclear magnetic resonance spectroscopy showed that brain phenylalanine was undetectable even though blood phenylalanine was 30 mg/dl. A second metabolic disorder may protect these patients from severe brain damage.

Conclusion These data indicate that brain damage in untreated or late treated patients with phenylketonuria is influenced by various genetic factors.

Key words Intelligence · Late treatment · Modifier gene · Phenylalanine hydroxylase · Phenylketonuria

Abbreviation *PKU* phenylketonuria

Introduction

Worldwide neonatal screening programmes for phenylketonuria (PKU) and other treatable disorders enable early treatment and prevention of mental retardation. However, some patients are missed in the newborn period. It is estimated that every 70th patient with PKU is not detected in the neonatal screening programme [2]. It is well known that initiation of dietary treatment in late treated patients with classical PKU is beneficial (for overview see [6]). More recently it also has

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been demonstrated that there is a positive effect with long-term treatment on the outcome of these patients [3].

The aim of this retrospective study in a cohort of 38 late treated patients from California reported by Koch et al. [3] was to evaluate the factors which predict the final IQ in these patients with PKU other than the quality and duration of treatment. Such data have practical relevance: (1) parents of late treated patients may be better informed about the prognosis of their child and (2) there would be better data available for the evaluation of the degree of brain damage, e.g. in negligence trials. In addition it may elucidate which other parameters may be relevant for the final outcome.

Subjects and methods

A total of 40 patients with classical PKU (blood phenylalanine >20 mg/dl without dietary treatment) who were detected later than 0.7 years of age were retrospectively evaluated. Inclusion criterion for statistical analysis were that patients were detected >0.7 and <7 years of age. Exclusion criterion was normal intelligence at an age older than 2 years even never having been treated. Thus a total of 38 patients were included. Psychological assessments were performed using the Wechsler Adult Intelligence Scale-Revised (WAIS-R) for adults, the Bayley tests (DQ) and the Stanford-Binet Intelligence quotient-Revised for infants and children respectively. Statistical analysis was performed by regression analysis using the JMP 3.2.2. program (SAS).

Results

Patient data are outlined in Table 1. Patient 1 (>7 years old when detected) and patients 32 and 40 (normal IQ at age >2 years without any treatment) were excluded from further calculation according to the criteria outlined above. Mean age at diagnosis was 2.44 years (range 0.7–7.0 years), mean plasma phenylalanine concentration was 27.5 mg/dl (range 17–43 mg/dl), final age at reinvestigation was 33.5 years (range 20–44 years).

Mean IQ/DQ at diagnosis was 52.7 (SD = 16.1), final IQ 79.0 (SD = 16.4); the difference was highly significant ($P < 0.0001$). There was a negative correlation between onset of treatment and initial IQ/DQ ($r = -0.46$, $P < 0.005$) (Fig. 1). However, there was a great fluctuation of the DQ in the first 2 years of life. The final IQ was also negatively correlated with the age when treatment was started. ($r = -0.42$, $P < 0.009$) (Fig. 2). Highest correlation was found for DQ/IQ at diagnosis and final IQ ($r = 0.51$, $P < 0.002$) (Fig. 3). IQ/DQ and final IQ respectively were not correlated with the concentration of blood phenylalanine at diagnosis.

Table 1 Patient data

Patient	Final age	Blood phenylalanine at diagnosis (mg/dl)	Age at diagnosis (years)	DQ/IQ at diagnosis final IQ	Increase in IQ	
1	43	23	5	47	78	31
2	44	23	4	43	53	10
3	41	39	1.3	68	87	19
4	39	21	2	29	59	30
5	39	23	1	43	61	18
6	39	18	2	48	85	37
7	38	19	2	–	85	–
8	37	31	2.5	40	88	48
9	37	21	1.5	66	98	32
10	37	26	4	58	88	30
11	35	29	5	52	77	25
12	33	29	1.5	53	87	34
13	33	29	4	29	55	26
14	32	34	2	65	75	10
15	29	20	7	43	73	30
16	25	26	5	42	70	28
17	25	26	1	50	85	35
18	24	17	4	62	77	15
19	24	39	1.5	48	98	50
20	23	36	4.5	42	94	52
21	22	27	2	40	96	56
22	21	36	1.5	70	108	38
23	21	35	2.5	46	73	27
24	20	21	3	38	67	29
25	40	28	1	30	–	–
26	39	21	6	25	35	10
27	39	22	1	–	51	–
28	36	40	0.75	84	90	6
29	35	27	4	50	60	10
30	35	30	1	60	70	10
31	35	30	1.5	53	86	33
32	35	20	4	109	99	–
33	35	30	1.5	97	78	–
34	33	40	0.7	59	102	43
35	41	43	1	65	67	2
36	40	20	1.5	–	97	–
37	37	24	1.5	49	84	35
38	36	20	0.75	75	86	11
39	32	23	0.7	76	102	26
40	28	30	24	100	100	

Discussion

The results confirm previous findings that dietary treatment is beneficial even in very late diagnosed patients with classical PKU. Koch et al. [3] showed that of 28 late but well and long-term treated patients with PKU, 18 could live independently and did not require residential care. Even though in our evaluation we did not consider quality and duration of dietary treatment, it could clearly be demonstrated that onset of dietary treatment is highly important. As expected, the earlier the diet is started the better the outcome.

Another important factor for the final outcome is the initial IQ. Our findings show that there is a positive correlation between the IQ/DQ at diagnosis and the final IQ in adulthood. The initial IQ may reflect the degree of brain damage the child has already developed. One may argue that dietary treatment may be more successful in patients having less severe brain damage. However, the increase in IQ was not related to the time when dietary treatment was started. Thus initial IQ has some prognostic value for estimating the final IQ.

There are, however, other factors than the plasma phenylalanine itself which may influence the final IQ. This is shown by patients 32 and 40 (Table 1) who had a

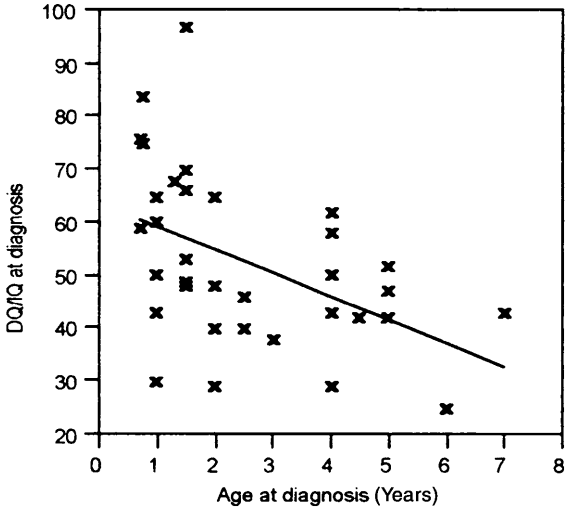

Fig. 1 Correlation (linear fit: DQ/IQ at diagnosis = 63.78–4.38 age at diagnosis; $r^2 = 0.22$) between DQ/IQ in 33 patients with untreated PKU and age at diagnosis

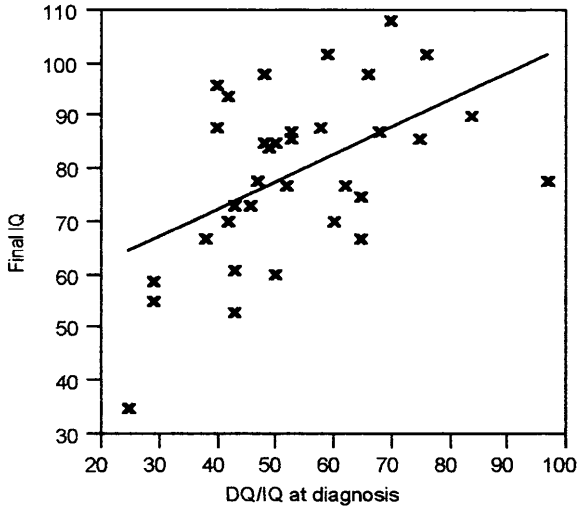

Fig. 3 Correlation (linear fit: final IQ = 51.73 + 0.51 DQ/IQ at diagnosis; $r^2 = 0.25$) between DQ/IQ in infancy/childhood and final IQ in adulthood in 33 late treated PKU patients

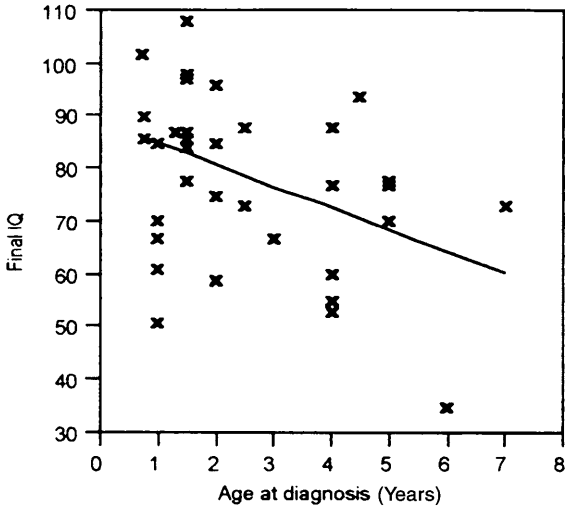

Fig. 2 Correlation (linear fit: final IQ = 89.30–4.14 age at diagnosis; $r^2 = 0.17$) between final IQ in 36 adult patients with PKU and age when dietary treatment was started

normal IQ of 99 at the age of 35 years and 100 at 24 years respectively despite never having been treated in their life. Normal IQs in non treated patients with classical PKU have been described in literature for many years (for overview see [1]). It is estimated that about 10% of patients with classical PKU may have intelligence within or near the reference range [1]. An explanation for this is still speculative. The findings from the group in Münster, Germany, may give some hints. They found in two patients with classical PKU and normal intelligence by in vivo magnetic resonance spectroscopy that brain phenylalanine was not correlated with plasma phenylalanine [5]. In both unaffected patients, brain phenylalanine was below the detection limit even when plasma phenylalanine was as high as 20 mg/dl. One of these two patients (patient 40, Table 1) was detected because of the typical symptoms of maternal PKU. At birth, the child had microcephaly and a severe heart defect. Plasma phenylalanine of the mother at that time was 30 mg/dl and genotype of the phenylalanine hydroxylase gene was R408W/R261Q indicating classical PKU. One may speculate that these patients with a normal brain phenylalanine may be protected by a second metabolic disorder, e.g. in the large neutral amino acid transporter which also transports phenylalanine across the blood-brain barrier. It may be that patient 32 (Table 1) also has the same condition. Recently, Pietz et al. [4] demonstrated that loading patients with classical PKU with large neutral amino acids decreases phenylalanine uptake into the brain and improves neurophysiological parameters. This is further evidence that the large neutral amino acid carrier may play an important role for intracerebral phenylalanine homeostatis.

In summary, final IQ in late treated phenylketonuric patients is influenced mainly by the age and the initial IQ when the phenylalanine restricted diet is started, however, other genetic factors may also have an impact on the final outcome.

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