PAPERS AND ORIGINALS

Effect of stopping low-phenylalanine diet on intellectual progress of children with phenylketonuria

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Summary and conclusions

Forty-seven patients at the Hospital for Sick Children, London, who had phenylketonuria and were on a low-phenylalanine diet (21 early-treated—that is, treatment started before the age of 4 months—and 26 late-treated) were placed on a normal diet between the ages of 5 and 15 years. They showed significant falls in mean IQ of about six points after the diet was withdrawn. Twenty-two similar patients (five early-treated and 17 late-treated) at the Universitäts-Kinderklinik, Heidelberg, who were placed on a relaxed low-phenylalanine rather than a normal diet, showed smaller and non-significant falls in mean IQ. During the period of strict diet none of the patients in London or Heidelberg showed any consistent falls in IQ.

These results suggest that complete withdrawal of the low-phenylalanine diet during childhood leads to a fall in intellectual progress in many patients.

Introduction

Most children with phenylketonuria who are treated with a low-phenylalanine diet from early infancy make normal or near-normal developmental progress.¹⁻⁴ It is agreed that

children with "classical" phenylketonuria should remain on the diet throughout the first two years of life while brain growth is rapid; for how long after this age the diet should be continued, however, is disputed. To add to our incomplete knowledge of this aspect of treatment we carried out a study to compare the experiences of two European treatment centres—namely, the Hospital for Sick Children, London, and the Universitäts-Kinderklinik, Heidelberg.^{5, 6}

Patients and methods

Treatment policies—At both centres the aim was to continue a strict low-phenylalanine diet until the children were at least 7 years old. Approaches to the management of the diet were similar,^{7, 8} but approaches to ending the treatment differed. In London, after a preliminary study in 1967 of nine patients over 8 years of age who received a normal diet for a trial period of six months,⁹ we stopped the diet in all patients when they reached 8 years.¹⁰ Parents were told to give a free diet without nutritional supplements. In Heidelberg the diet was continued for as long as the patients could adhere to it without undue difficulty. When difficulties occurred the diet was relaxed rather than stopped and a wider range of normal food permitted. The degree of relaxation varied with the patient's ability to adhere to the restrictions. We tried to keep blood phenylalanine concentrations below 1200 $\mu\text{mol/l}$ (19.8 mg/100 ml), and a supplement of phenylalanine-free L-amino-acids (1 g/kg/day) was prescribed for each child.

Case selection—All patients who had been treated with a strict diet for at least three years and had started treatment before 5 years of age were included if they were over 8 years old at the time of the study and if their blood phenylalanine concentrations had risen above 900 $\mu\text{mol/l}$ (14.2 mg/100 ml) on a normal diet. No further attempt was made to distinguish variants of the disorder. We refer to children who started the diet before 4 months of age, after diagnosis by neonatal screening, as "early-treated"; those who started the diet after 4 months of age, the diagnosis having been made because of symptoms, are referred to as "late-treated."

Clinical and biochemical data—Clinical information was extracted from the case notes. Routine measurements of blood phenylalanine concentrations had been made using the Guthrie technique,¹¹⁻¹³ a semi-quantitative microbiological assay. This technique, although useful for routine purposes because of its cheapness and simplicity, provides a less precise measure of phenylalanine concentrations than,

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for example, fluorimetry,¹⁴ especially when the concentrations are above 1200 $\mu\text{mol/l}$ (19.8 mg/100 ml).

IQ data—We recorded from the record forms IQs that had been measured after the age of 3 years, the complete form of the Revised Stanford-Binet Test (SB; Form L-M, used for children under 6.5 years) or the Wechsler Intelligence Scale for Children (WISC), or their German equivalents, the Revised Binet-Kramer and the Hamburg-Wechsler Intelligenz Test für Kinder (HAWIK), having been used.

Analysis of results—Late-treated patients with IQs below 46 were excluded from the main analysis (12 patients in London and three in Heidelberg), as was the London patient in whom diet was stopped at the age of 3. These cases are described separately. The remaining patients were divided into five groups as follows: London—group I, early-treated, normal diet (21 cases); group II, late-treated, normal diet (26); Heidelberg—group IIIa, early-treated, relaxed diet (21); group IIIb, early-treated, still on strict diet (9); and group IV, late-treated, relaxed diet (17). To examine the effect of a change in diet on intellectual progress we carried out a series of paired *t*-test comparisons of mean IQ. We also investigated the relations between change in IQ and age at diet change and between change in IQ and IQ before diet change by calculating product moment correlation coefficients.

Results

Age and duration of treatment—The mean ages of the patients from the two centres at the start of treatment were closely similar, being under 6 weeks for early-treated (groups I, IIIa, and IIIb) and just under 2 years for late-treated patients (groups II and IV). Although no age had been specified for the relaxation of the diet in Heidelberg, the average age at diet change there was similar to the age at which the diet was stopped in London (early-treated groups I and IIIa 97.9 and 94.2 months, late-treated groups II and IV 125.0 and 107.4 months). Nine early-treated children in Heidelberg (group IIIb), however, were still being treated with strict diet at an average age of 10.1 years. The average age at diet change was greatest and the scatter of ages widest in the late-treated London patients.

Phenylalanine concentrations—Median phenylalanine concentrations were between 360 and 480 $\mu\text{mol/l}$ (5.9 and 7.9 mg/100 ml) in the last year before the change in diet (groups I, II, IIIa, and IV). Heidelberg patients still supposed to be on a strict diet (group IIIb) had median phenylalanine concentrations of 720 $\mu\text{mol/l}$ (11.9 mg/100 ml) in the last year of follow-up, suggesting that they adhered to the diet less strictly as they grew older. After the diet change the London patients had median phenylalanine concentrations consistently above 1200 $\mu\text{mol/l}$ (19.8 mg/100 ml). Heidelberg patients in whom the diet was relaxed rather than stopped (groups IIIa and IV) showed a smaller and more gradual rise in phenylalanine concentrations, these being 780 and 900 $\mu\text{mol/l}$ (12.9 and 14.9 mg/100 ml) in the first year; 1050 and 900 $\mu\text{mol/l}$ (17.3 and 12.9 mg/100 ml) in the second; 1050 and 1050 $\mu\text{mol/l}$ (17.3 mg/100 ml) in the third; and 1200 and 1050 $\mu\text{mol/l}$ (19.8 and 17.3 mg/100 ml) in the fourth years after diet change.

IQ changes occurring during treatment with strict diet—There was a significant rise in mean IQ of nine points between the first IQ measured after 3.0 years of age and the last measured before 8.9 years in the late-treated Heidelberg children (group IV). None of the other groups showed significant changes in mean IQ. Patients remaining on the diet after 8.9 years showed no significant falls in IQ between the last IQ measured before 8.9 years and the last IQ measured before diet change (groups I, II, and IIIa showed rises of 3.5, 0.7, and 2.2 points, and group IV showed a fall of 2.4 points).

Comparison between last IQ measured while patients on strict diet and IQs measured after diet change (table I)—The interval between the last IQ test while the children were on strict diet and the first after diet change was longer in the London than the Heidelberg cases; the longest interval was in group II. Between the last IQ test on strict diet and the first after diet change there was a fall in mean IQ in groups I, II, and IV; between the last IQ test on strict diet and the first IQ measured at intervals of more than one, two, and three years after diet change there were consistent falls in mean IQ in all groups. These falls were greatest in the London groups (I and II) and reached significance only in these groups. Early-treated cases (groups I and IIIa) showed a progressive fall in IQ as the interval between diet change and IQ assessment lengthened.

Relations between change in IQ and age and IQ at diet change—Late-treated patients tended to be older at diet change than early-treated patients. Those in group II had the highest average age at

TABLE I—Comparison between last IQ measured while children on strict diet and first IQ measured after (1) diet change, (2) interval of more than one year after diet change, (3) interval of more than two years, and (4) interval of more than three years. Mean interval between change in diet and IQ test and mean age at test also shown

Group	Com- parison	No of patients	Mean IQ ($\pm$ SD)		Change in IQ	Mean interval between diet change and IQ test (months)	Mean age at IQ test after diet change (months)	
			On diet	After diet change				
London								
I	{	1	21	96.3 $\pm$ 13.2	90.8 $\pm$ 15.9	-5.5*	26	124
		2	20	95.8 $\pm$ 13.3	89.6 $\pm$ 14.7	-6.2*	30	129
		3	16	95.3 $\pm$ 14.7	87.6 $\pm$ 14.1	-8.3***	34	134
		4	7	95.8 $\pm$ 16.6	86.7 $\pm$ 19.3	-9.1*	44	158
II	{	1	26	74.3 $\pm$ 13.4	68.9 $\pm$ 12.3	-5.3**	36	163
		2	20	74.3 $\pm$ 13.0	69.5 $\pm$ 11.9	-4.8*	39	165
		3	16	75.1 $\pm$ 13.6	69.7 $\pm$ 11.8	-5.4	46	171
		4	10	73.8 $\pm$ 15.6	70.0 $\pm$ 14.2	-3.8	60	180
Heidelberg								
IIIa	{	1	5	105.8 $\pm$ 9.2	107.4 $\pm$ 11.7	+1.6	8	116
		2	5	105.8 $\pm$ 9.2	103.0 $\pm$ 17.5	-2.8	26	120
		3	5	105.8 $\pm$ 9.2	101.1 $\pm$ 11.2	-4.8	36	130
		4	3	109.7 $\pm$ 10.5	103.3 $\pm$ 11.4	-6.7	47	140
IV	{	1	17	77.6 $\pm$ 17.4	74.0 $\pm$ 14.1	-3.6	9	116
		2	14	76.0 $\pm$ 18.1	74.3 $\pm$ 16.3	-1.7	20	129
		3	8	73.0 $\pm$ 14.6	71.0 $\pm$ 13.8	-2.6	34	138
		4	5	74.6 $\pm$ 16.4	70.2 $\pm$ 17.2	-4.4	48	154

P* < 0.05; *P* < 0.01; ****P* < 0.001 by paired *t* test.

TABLE II—Effect of age under and over 9 years on change in IQ after withdrawal of strict diet in groups II and IV. Comparisons are between last IQ measured while children on strict diet and first IQ measured after (1) diet change, (2) interval of more than one year after diet change, (3) interval of more than two years, and (4) interval of more than three years

Group	Comparison	Aged < 9 years		Aged $\geq$ 9 years	
		No of patients	Change in IQ	No of patients	Change in IQ
II	1	11	-8.0**	15	-3.3
	2	10	-7.7**	10	-1.8
	3	8	-9.0*	8	-1.7
	4	5	-5.4	5	-2.2
IV	1	7	-3.2	10	-3.6
	2	6	-3.0	8	-0.9
	3	4	-4.5*	4	+0.5
	4	2	-5.5	3	-3.7

P* < 0.05; *P* < 0.01 by paired *t* test.

diet change as well as the widest age scatter, and in this group the average age at the first IQ test after diet change was already greater than the average age of the other groups at the end of the follow-up period (table I). Only in group II was there a significant correlation between IQ change (last IQ on strict diet minus first IQ after diet change) and age at diet change ($r = +0.52$, $P < 0.01$). Group II was also the only one to show a significant correlation between IQ change and the last IQ measured on strict diet ($r = -0.41$, $P < 0.01$). These correlations imply that in group II the younger the child and the higher the IQ at diet change the greater the fall in IQ. When a partial correlation coefficient is calculated for IQ change and age at diet change, allowing for IQ at diet change, a significant correlation persists ($r = +0.49$, $P < 0.01$). When group II was divided into patients who stopped taking the diet before and after 9 years of age (table II), those who were older at diet change showed small and non-significant changes in mean IQ, whereas those who were under 9 years showed larger falls, which reached significance. Group IV, the only other group with enough patients over 8.9 years at diet change for comparison to be made, showed no such clear-cut association between IQ change and age.

Relation between IQ change and blood phenylalanine concentrations after diet change—London patients had blood phenylalanine concentrations above 1200 $\mu\text{mol/l}$ (19.8 mg/100 ml) after being placed on a free diet and showed significant falls in mean IQ, whereas the Heidelberg patients in groups IIIa and IV had blood phenylalanine concentrations mostly below 1200 $\mu\text{mol/l}$ after being placed on a relaxed diet and showed either small and non-significant falls in mean IQ or, in one case, a rise. Because of the inaccuracy of the Guthrie

technique when phenylalanine concentrations are above 1200 $\mu\text{mol/l}$ it was not possible to examine the relation between the concentrations and IQ change in any greater detail.

Intellectual changes in patients excluded from the main analysis—Thirteen of the 15 severely retarded patients showed falls in tests of intellectual level. Many children showed an actual loss of intellectual skills—for example, a fall in scaled-scores of patients tested on the WISC—as well as a fall in intellectual progress. One London patient, who was placed on a normal diet when he was 3, showed no fall in intellectual progress after withdrawal of the diet. At 2½ years he had a Griffiths Developmental Quotient of 80-90; his IQs at 5 years of age (83, SB) and at 7 and 9 years (88 and 91, WISC) suggest, if anything, a rise in intellectual ability.

Discussion

Falls in mean IQ of five to nine points occurred in the London patients after a normal diet was introduced. The consistently negative direction of the changes, their statistical significance, and the progressive fall in mean IQ of early-treated patients suggest that London patients suffered a real fall in intellectual progress. Patients in Heidelberg, with the exception of one whose results were just significant at the 5% level, showed no significant falls in mean IQ after withdrawal of the strict diet. The changes were once again negative, however, apart from a small positive change between the last IQ on diet and the first measured after diet change in the early-treated patients. At that stage these patients had shown only a small rise in blood phenylalanine concentration; they subsequently showed a progressive fall in IQ as the phenylalanine concentrations rose further. These results suggest that even the Heidelberg patients on a relaxed diet may have suffered some slowing of intellectual progress, although of a less severe degree than the London patients.

As there was no control group of patients in whom strict diet was continued, it remains uncertain whether the association between diet change and IQ change is causal. The absence of any significant falls in IQ during the period of strict diet, and in particular the absence of any such falls after the age of 8-9 years, supports the view that withdrawal of the strict diet was responsible for the IQ changes. The occurrence of larger falls in London patients, in whom diet was withdrawn completely, than in Heidelberg patients in whom the diet was only relaxed is also compatible with a cause and effect relation. Falls in IQ due to withdrawal of the strict diet might be expected to be greater the younger the child. A negative association was found between IQ change and age at diet change among the late-treated London children, the only group with a wide scatter of ages at diet change. Early-treated patients, who were younger and had a narrower age range at diet change, showed instead a progressive fall in IQ after diet change, while the late-treated patients, who were older, showed no further fall after an initial drop in IQ.

Other studies have observed falls in IQ,¹⁵⁻¹⁸ electroencephalographic changes,¹⁷⁻¹⁹ behavioural deterioration,^{9 20 21} and even frank neurological illness²² after withdrawal of the strict diet. Not uncommonly parents comment on the wild behaviour of the children when a normal diet is first introduced, and two studies^{9 20} have documented such behaviour changes. Adding L-phenylalanine to the phenylalanine-restricted diet may lead to ataxia and drowsiness when blood phenylalanine concentrations exceed 240 $\mu\text{mol/l}$ (39.6 mg/100 ml).⁷ This phenomenon was noted by Bickel *et al* in describing the use of a low-phenylalanine diet.²³ Even normal subjects and those heterozygous for phenylketonuria may show changes in cognitive ability when their blood phenylalanine concentrations are raised by loading with L-phenylalanine.²⁴ This suggests that phenylalanine accumulation may have acute effects on intellectual function as well as long-term effects.

Some studies have found no ill effects of dietary withdrawal.²⁵⁻²⁷ A formal trial of stopping diet in patients at the age of 4 years has been set up, and preliminary findings on five pairs of children have so far shown no difference in intellectual

progress between the children in whom diet was continued and those put on a normal diet.²⁸ Thus evidence concerning the effect on intellectual progress of stopping the low-phenylalanine diet is conflicting. Nevertheless, the studies in which falls in IQ have occurred after dietary withdrawal have been those with larger numbers of patients, who have been followed up for longer periods and have had relatively strict control of blood phenylalanine concentrations up to the change in diet. The quality of dietary control before stopping the diet may be an important factor: if introduction of a normal diet does lead to intellectual deterioration then poor control during treatment might obscure any effect of dietary withdrawal on IQ.

Several reports suggest that patients with phenylketonuria, even those treated from early infancy, have mean IQs slightly below those expected for the general population and for their families.^{4 29 30} This might be explained by less than optimal dietary control. Data from the National Phenylketonuria Register in the UK show that there is an inverse relation between IQ at 4 years of age and mean phenylalanine concentrations during the fourth year.³¹ A similar observation was made by Brown and Warner.¹⁸ Electroencephalographic abnormalities have also been associated with raised blood phenylalanine concentrations during the middle years of childhood.¹⁹ These findings are consistent with the view that, even after infancy, moderately raised concentrations may still impair cerebral function. On the other hand, a prospective study designed to compare IQ at the age of 3 years between patients treated with a strict diet (concentrations of 60-300 $\mu\text{mol/l}$ (1-5 mg/100 ml)) and a more liberal diet (300-600 $\mu\text{mol/l}$ (5-10 mg/100 ml)) failed to show a difference.² This study did not, however, achieve clear-cut separation between the phenylalanine concentrations of the two groups.

As a result of preliminary findings in London the policy of stopping diet completely at the age of 8 was changed in 1975 to one of relaxing diet at that age. Patients reaching 8 years are placed on a diet that keeps blood phenylalanine concentrations between 900 and 1200 $\mu\text{mol/l}$ (14.8-19.8 mg/100 ml) and includes a supplement of L-amino-acids (1 g/kg/day). From the Heidelberg results presented here there is some evidence that even relaxation of the diet may be associated with falls in IQ, and, in contrast to views expressed previously,¹⁰ it can now be argued that children with phenylketonuria should be kept on a strict diet for as long as they will accept the restrictions willingly or until the safety of stopping it has been shown. In practice, however, as the Heidelberg results show, not all patients can be kept on a strict diet throughout later childhood, although since 1976 a relaxed diet has not been introduced before the age of 10.

More data are needed to decide whether at a particular age intellectual deterioration is to be expected when a normal or relaxed diet is introduced. In our opinion the available evidence, including the data presented here, suggests that introduction of a completely normal diet before the age of 8 leads to some intellectual deterioration in many but not all patients. The occurrence and severity of such deterioration probably depend on several factors, including the child's age, the quality of dietary control before diet change, the type of phenylketonuria, and individual variations.

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Two types of febrile seizure: anoxic (syncopal) and epileptic mechanisms differentiated by oculocardiac reflex

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Summary and conclusions

The duration of cardiac asystole induced by ocular compression was measured in 100 consecutive children referred for electroencephalographic examination after one or more febrile convulsions (FC). The children were classified into three groups—namely, those with anoxic FCs, those with epileptic FCs, and “others”—according to the appearances of the FC and the electroencephalogram (EEG). In 14 children the description of the FC suggested non-epileptic anoxic cerebral seizures such as are seen after prolonged syncope or breath-holding. In 35 children the FCs were assumed to be epileptic in mechanism on the basis of unilateral (hemiclonic) twitching, known cerebral disease, a family history of epilepsy, or spikes on the EEG. In the 51 “others” the FCs could not be classified. Definitely abnormal asystole (four seconds or over) was induced by ocular compression in half the anoxic group, in 16% of the “others,” but in none of the epileptic group. The differences between the degree of asystole induced in each of the three groups was highly significant ($P=0.005$).

These results support the hypothesis that vagal-mediated cerebral ischaemic anoxia is implicated in the genesis of FCs that resemble anoxic seizures and in a substantial number of those without an obvious epileptic mechanism. The significance, genetics, management, and prognosis of FCs must now be re-examined in this light.

Introduction

Febrile convulsion (FC) is the most common neurological disorder of childhood.¹ It is frightening to witness, and may sometimes lead to lasting brain damage,^{2,3} but exactly what it is and why it affects only certain children are ill understood. It is usually assumed⁴⁻⁶ that FCs are epileptic in mechanism—that is, that they result from excessive hypersynchronous cerebral neuronal discharges⁶—even though epilepsy rarely follows in later life.⁷ An alternative suggestion^{8,9} that the convulsions are primarily anoxic or syncopal—that is, that they are associated with reduced cerebral blood flow and reduced cerebral cortical neuronal activity⁶—has been almost totally ignored.¹⁰ In a recent study¹¹ of reflex anoxic seizures presumed to result from vagal-mediated cardiac arrest after unpleasant stimuli¹² the retrospective incidence of FCs was 14%, four times the expected incidence of 3.4%⁷ ($P<0.002$). Furthermore, the FCs in that study did not appear from the history to differ in character from afebrile reflex anoxic seizures suffered by the same children. I have therefore carried out a study to investigate prospectively a series of children with a history of FCs, first making a clinical judgment on the type of FC—whether anoxic, epileptic, or uncertain—and then using a physiological technique¹¹ that elicits the oculovagal or oculocardiac reflex, which is hypersensitive in syncope,¹³ to differentiate between reflex anoxic and epileptic seizures.

Patients and methods

I studied 100 consecutive children aged under 8 years referred to the electroencephalography department with a history of FCs (defined as any seizure with fever of 38°C or over). There were no exceptions, as those who also had, for example, afebrile seizures or cerebral disease were included. Before the study, in accordance with hospital policy, children who had had FCs and were referred for electroencephalographic examination were mostly atypical or had had recurrences. During the study there was an increased referral

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