ORIGINAL ARTICLE

Effects of dietary management of phenylketonuria on long-term cognitive outcome

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Background: Phenylketonuria (PKU) is associated with dopaminergic depletion in the dorsolateral prefrontal cortex and abnormalities of myelination. Both mechanisms may lead to deficits in cognitive functioning. Studies of cognitive outcome in children treated with PKU at an early stage have suggested that there are benefits in remaining on diet into adolescence.

Aim: To assess the nature and extent of any cognitive deficits in adults treated at an early stage with PKU who had discontinued their diets in adolescence.

Method: 25 patients (aged 18–38 years) who were diagnosed early and had discontinued their diets in adolescence were compared with 25 adults (aged 18–38 years) with PKU on continuous diet, and with a healthy control group (n = 45).

Results: The groups differed significantly on accuracy (p = 0.007) and speed (p = 0.001) of performance on an n-back working memory task and on speed of performance (p = 0.001) on a flanker inhibitory task, but not on flanker accuracy, object alternation learning or perceptual judgement tasks (all p > 0.05). The off-diet group performed significantly below the on-diet group on n-back accuracy (p = 0.007) and flanker speed (p = 0.05), and significantly below the control group on n-back speed (p = 0.002) and flanker speed (p = 0.001).

Conclusion: The findings suggest that although discontinuing diet in adolescence appears disadvantageous compared with remaining on continuous diet, any deficits are relatively subtle.

Phenylketonuria (PKU) is caused by the deficiency of phenylalanine hydroxylase, which converts phenylalanine (Phe) into the dopamine precursor tyrosine. Without treatment, PKU generally results in severe learning and behavioural disturbances.¹ Early screening and effective dietary treatment have considerably improved outcomes,² such that children treated early can now expect to lead relatively normal lives, although mean IQ scores for children with PKU in the UK have been shown to be below the population means.³ Relationships have been reported between IQ and factors such as treatment initiation, duration and severity of exposure to Phe in early childhood.^{3–4} A minority of adults with PKU showed increased psychosocial morbidity,⁵ and this has been linked to poorer performance on measures of intellectual and executive functioning.

Two main hypotheses were proposed regarding the possible mechanisms leading to cognitive impairment in PKU—namely, slowed information processing resulting from deficient white matter myelination, and selective executive deficits associated with prefrontal cortex (PFC) dysfunction resulting from neurotransmitter abnormalities. Both white matter abnormalities and PFC dysfunction may occur together in PKU.⁶ Abnormalities of myelination have been linked to PKU,^{2,6} particularly in posterior and periventricular white matter. Neurotransmitter abnormalities have also been identified. Tyrosine deficiency may lead to deficiency of dopamine; and increased Phe impedes transport of other amino acids into the brain. Indeed, dopamine neurones in the ventral tegmental area projecting to PFC may be differentially depleted through this process.^{7–8} The frontal lobes, particularly the PFC, are believed to be central to executive functions, which control our ability to respond adaptively to the environment by orchestrating necessary cognitive processes to achieve specific goals.⁹ Dopamine plays a central role in functions linked with the

lateral PFC.¹⁰ These include working memory, attentional control and inhibition of habitual responses.

Available evidence for children with PKU does not differentiate clearly between these two hypotheses. Studies have varied considerably in terms of methods, making comparisons difficult. White *et al*⁶ described reduced processing speed in children treated early with PKU, and linked this to white matter abnormalities. Several studies have examined the executive deficit hypothesis using measures involving working memory, sustained attention or inhibition. Some reported executive dysfunction despite a normal IQ, even with continuous dietary treatment.^{6,8,11–14} Other studies have failed to find deficits.^{15–18} Welsh¹⁹ noted it was not clear whether executive impairment continued into adulthood, or simply showed a developmental lag that eventually disappeared with continued treatment.

Little work has been performed examining the outcome in adult patients who were adequately treated from an early age, and little is known about the possible benefits of lifelong treatment. There are two key questions: what mechanisms underpin any cognitive deficits in adults with PKU; and are there continuing benefits in staying on a lifelong diet? Some support has been provided for selective executive deficits,¹⁸ but other findings have been mixed. Ris *et al*²⁰ studied a group of adults on and off diet and reported deficits compared with controls in IQ, attention and visuoconstructional ability, but not on an executive task. Impairment was found both on executive and non-executive clinical tasks in adults with PKU who were off diet or poorly controlled.²¹ In two previous studies, we examined the outcome in adults with PKU who were treated early and put on lifelong diet, and found only mild

Abbreviations: ANOVA, analysis of variance; PFC, prefrontal cortex; Phe, phenylalanine; PKU, phenylketonuria

impairment in aspects of cognitive functions, with little evidence of a selective executive deficit on either clinical²² or computerised experimental²³ tasks. The present study was designed to investigate outcomes in off-diet adults with PKU who were diagnosed early and treated. It was hypothesised that they would show subtle cognitive impairments, but that these would not reflect selective executive deficits.

METHODS

Ethical approval was obtained from the UCL ethics committee.

Off-diet PKU group

All those with PKU attending the Metabolic Clinic at the National Hospital for Neurology and Neurosurgery, London, UK, were screened to identify those diagnosed and started on a low Phe diet within 1 month, remaining on diet for at least 10 years and discontinuing diet for at least 5 years afterwards. Remaining on diet was defined as continuing to restrict intake of natural protein and taking amino acid, vitamin and mineral supplements. Discontinuing diet involved stopping supplements and increasing natural protein intake. The exclusion criteria included diagnosis of a neurological disorder, psychiatric illness or lack of fluency in English. In all, 25 participants met the selection criteria (17 men, 8 women; age range 18–38 years). Twenty three subjects had classical PKU (off diet Phe >1200 µmol/l) and two had atypical PKU (off diet Phe 600–1199 µmol/l).

On-diet PKU group

The off-diet group was compared with 25 patients (13 men and 12 women; age range 19–35 years) with PKU who started on diet within 1 month and remained on diet continuously. These have been reported previously.²³ Twenty four subjects had classical and one atypical PKU.

Control group

Comparison was made with a group of 45 controls (26 men and 19 women; age range 20–47 years), consisting of 25 people recruited previously²³ and 20 new recruits.

Clinical measures

Participants were screened using the structured clinical interview for diagnostic and statistical manual of mental disorders,²⁵ and none met the criteria for major psychiatric disorders. Other measures included IQ (Wechsler abbreviated scale of intelligence (WASI))²⁴; Beck anxiety inventory²⁶; Beck depression inventory²⁷; short form SF36v2 quality of life questionnaire²⁸; self-report and relevant other versions of the Dysexecutive Questionnaire.²⁹

Measures of metabolic control

Phe data were collected from the medical notes. Some variation was observed in the method of Phe measurement used, as several different laboratories had been involved and methods had altered over the lifespan of the participants. Phe data were based on Guthrie bloodspot tests and/or blood levels, depending on the availability; data were missing for some participants. Annual median Phe levels were used to calculate means for each 4-year period from birth. Other measures were “concurrent Phe”, using the most recent level, and “recent Phe”, using the mean level for the year preceding testing.

Experimental measures

A series of computerised tests were conducted, outlined below, with computerised scoring of correct responses and median reaction times for correct responses. Detailed descriptions of the tests and scoring are contained in Channon *et al.*²³

Attention and working memory

An adapted version²³ of the n-back test³⁰ was used to compare performance on three conditions with increasing working memory load (0-back, 1-back, 2-back). Functional imaging has shown that activation of the dorsolateral PFC increases with memory load.³¹ All conditions required participants to press a “Yes” or “No” response key as quickly as possible, in response to letters presented individually on the computer screen. In the delayed response conditions, participants were required to compare the current letter with the previous letter (eg, DD or XX, 1-back) or with the one before last (eg, DXD or XDX, 2-back), and respond “Yes” when the two letters match, or “No”; trials are biased towards “No” responding.

Table 1 Mean scores and standard deviations for the demographic measures

Variables	Group						p Value
	Control (n = 45)		PKU off diet (n = 25)		PKU on diet† (n = 25)		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Demographic and IQ measures							
Age	28.76	(7.46)	27.48	(4.55)	26.68	(4.92)	*
Years of education	13.47	(1.87)	13.08	(2.12)	14.44	(1.87)	
WASI full scale IQ	106.98	(8.9)	101.48	(14.60)	107.04	(12.01)	
Age diet discontinued	—		14.84	(3.09)	—		
			(range 10–24)				
Clinical measures							
Beck anxiety inventory	2.89‡	(4.89)	3.64	(3.93)	3.32	(4.96)	
Beck depression inventory	3§	(4.76)	3.48	(3.73)	2.80	(4.51)	
SF36v2 quality of life mental	51.97‡	(7.33)	51.35**	(7.31)	51.58	(6.97)	
SF36v2 quality of life physical	56.67‡	(3.3)	55.28**	(4.72)	56.48	(4.17)	
DEX self-ratings	11.63‡	(9.35)	12.32	(7.3)	11.12	(7.33)	
DEX other-ratings	10.34¶	(8.77)	14.09††	(9.33)	10.05††	(8.99)	

DEX, dysexecutive; PKU, phenylketonuria; WASI, Wechsler Abbreviated Scale of Intelligence.

*p < 0.05

†PKU on-diet group from Channon *et al.*²³

‡n = 43.

§n = 44.

¶n = 38.

**n = 24.

††n = 22

Inhibition

Imaging evidence indicates activations including the anterior cingulate and ventrolateral PFC to stimulus-response conflict such as that produced by the flanker task,³² based on Eriksen and Eriksen³³ and adapted.²³ It consisted of five arrows (one central arrow and two “flankers” to either side). On conflict trials, the central arrow and flanker arrows pointed in opposite ways, requiring suppression of interference from the flanker arrows when responding to the central arrow.

Object alternation learning

Object alternation learning is sensitive to perseverative responding after orbitofrontal and medial lesions.³⁴ An adapted version²³ was used. Two boxes were presented, and a reward was hidden under one of them. The box opened to display a coin when the choice was correct, and was empty for incorrect choices.

Perceptual judgement

In this task, participants were asked to match objects according to similarity of physical shape or similarity of object function using the Birmingham object recognition battery.³⁵

The off-diet PKU group was compared with the on-diet PKU and control groups on the demographic, clinical and experimental measures using analysis of variance (ANOVA), with post hoc Scheffé comparisons for significant results. Pearson correlations were used to examine the relationships between cognitive performance and metabolic function.

RESULTS

Demographic and clinical measures

ANOVA showed that the three groups did not differ significantly in age or Wechsler Abbreviated Scale of Intelligence full-scale (IQ) ($p > 0.05$), or on clinical measures: Beck anxiety scale, Beck depression scale, short form-36 mental or physical ratings, or Dysexecutive-self or other ratings ($p > 0.05$; table 1). They did differ in years of education, $F_{2,92} = 3.35$, $p = 0.039$. Post hoc Scheffé tests showed that the off-diet PKU group received fewer years of education than the on-diet group ($p = 0.051$). Table 2 shows mean Phe concentrations over time for the two PKU groups, and the number of participants with missing data for each time period. T tests showed that they did not differ significantly in Phe concentrations aged 1–4 years. The off-diet group had higher mean Phe concentrations than the on-diet group over each 4-year period from age 5 to 8 years ($p < 0.05$), and the mean scores showed that these differences increased with age.

Cognitive measures

Table 3 shows the mean scores and standard deviations (SD) for the three groups.

Attention and working memory

On the n-back task, ANOVA comparing accuracy of performance on 0-back, 1-back and 2-back conditions showed no significant group by condition effect ($p > 0.05$), but a significant effect of group, $F_{2,92} = 5.31$, $p = 0.007$. Post hoc Scheffé tests showed the off-diet PKU group to be less accurate than the on-diet PKU group across conditions ($p = 0.007$); neither the off-diet nor the on-diet PKU groups differed from the control group. When speed of performance was examined using logarithmically transformed scores, there was no significant group by condition effect ($p > 0.05$), but the effect of group was again significant, $F_{2,92} = 8.6$, $p = 0.001$. Post hoc Scheffé tests showed the off-diet PKU group to be slower than controls across conditions ($p = 0.002$); the on-diet PKU group was also

slower than the controls ($p = 0.009$); the two PKU groups did not differ significantly.

Inhibition

On the flanker task, for ANOVA comparing accuracy of performance on the compatible and incompatible trials, the group by trial-type effect (inhibition) and the group effect were not significant ($p > 0.05$). When speed of performance was examined using logarithmically transformed scores, the group by trial-type effect was not significant, but the effect of the group was ($F_{2,92} = 9.27$, $p = 0.001$). Post hoc Scheffé tests showed that the off-diet PKU group was slower than controls ($p = 0.001$) and on-diet PKU participants ($p = 0.05$) across conditions; the on-diet group did not differ significantly from controls.

Object alternation learning

On the alternation-learning task, ANOVA showed no significant differences between the groups in the ability to learn the correct alternation rule, as judged by the percentage of correct trials, or the percentage achieving 10 consecutive correct trials; nor did they differ significantly in speed of performance ($p > 0.05$ for all tests).

Perceptual judgement

ANOVA comparing the groups on the two perceptual judgement tasks showed no significant group by task effect or effect of group for either accuracy or speed of performance ($p > 0.05$ for all tests).

Relationship with metabolic measures

To examine relationships between performance on metabolic measures for the off-diet PKU group and cognitive tasks that significantly differentiated the groups, Pearson correlations were calculated between variables and concurrent Phe concentrations, recent Phe and lifelong Phe concentrations for each 4-year period, using $p = 0.01$ (table 4). No significant correlations were observed between cognitive measures and most metabolic measures. Speed on the 0-back task correlated significantly with Phe aged 1–4 years ($r = -0.58$, $p < 0.01$), and speed on the 2-back task correlated significantly with Phe aged 13–16 years ($r = -0.54$, $p < 0.01$), but both correlations were in the unexpected direction—that is, faster speed correlated with higher rather than lower Phe concentrations. Speed on the 0-back correlated significantly in the expected direction with concurrent Phe ($r = 0.55$, $p < 0.01$). Correlations with age of stopping diet were examined, but these were not significant with cognitive measures. For the on-diet group, there was only one significant correlation,²³ speed on the 0-back task and Phe levels aged 5–8 years ($r = 0.56$, $p < 0.01$), in the expected direction.

DISCUSSION

The current study assessed outcomes in early-treated adults with PKU off-diet for at least 5 years. As expected, they showed subtle cognitive impairments relative to controls, performing below the controls in speed but not accuracy on the n-back and flanker tasks. There was little support for a selective executive deficit, as there was no evidence of impairment on measures relatively independent of executive processes (object alternation learning, perceptual judgement), and performance was not selectively affected only by the executive components of measures sensitive to the executive processes.

Comparison was also made with an early-treated PKU group²³ on lifelong diet, to see whether a diet-for-life policy conferred advantages. The off-diet group received fewer years of education than the on-diet group, although the reasons for

Table 2 Mean scores and standard deviations for the metabolic measures for the off-diet and on-diet groups with PKU

Variables	Group						p Value
	PKU off diet (n = 25)			PKU on diet† (n = 25)			
	Mean	(SD)	(Range)	Mean	SD	Range	
Mean Phe level age 1–4‡	460.59‡	(181.91)	(171.75–786.69)	450.58§§	(123.97)	(255.75–727.5)	
Mean Phe level age 5–8‡	586.5§	(199.91)	(276–986.25)	456.85§§	(127.3)	(237.13–740)	*
Mean Phe level age 9–12‡	917.69	(209.53)	(430–1380)	697.3§§	(280.65)	(175–1275)	*
Mean Phe level age 13–16§	1153.24‡	(242.91)	(859–1710)	775.7‡	(255.9)	(422.25–1411.5)	*
Mean Phe level age 17–20§	1345.79§	(282.26)	(845–2013)	867.73‡	(248.89)	(448–1443.13)	*
Mean Phe level age 21–24¶	1362.55**	(268.87)	(850–1774.5)	850.74§	(229.44)	(323.75–1216.81)	*
Mean Phe level age 25–28**	1408.19††	(426.96)	(989–2815.5)	868.63¶¶	(187.4)	(572–1170.09)	*
Mean Phe level age 29–32††	1320.46‡‡	(262.99)	(995–1736)	795.75***	(228.62)	(470.32–1194.25)	*
Concurrent Phe levels§	1285.68	(197.83)	(990–1651)	758.79‡	(261.27)	(221–1233)	*
Recent Phe levels§	1317.77	(221.78)	(1013.67–1710)	797.62‡	(240.8)	(283.4–1153)	*

Phe, phenylalanine; PKU, phenylketonuria.

*p<0.05.

†PKU on-diet group from Channon *et al.*²³

‡n = 24.

§n = 23.

¶n = 22.

**n = 17.

††n = 19.

‡‡n = 15.

§§n = 21.

¶¶n = 16.

***n = 12.

this are unclear. The off-diet group performed significantly below the on-diet PKU participants on n-back accuracy and flanker speed. The on-diet group performed below the controls only on n-back speed, as shown by Channon *et al.*²³ We found no noticeable differences between the groups in psychosocial morbidity, suggesting that any difficulties shown by the PKU

participants were not mediated by differences in psychiatric symptomatology.

Comparison of the metabolic data showed that the on-diet and off-diet PKU groups did not differ significantly in early childhood. The off-diet group had higher Phe levels from age 5–8 years onwards, even though none had discontinued diet at

Table 3 Mean scores and standard deviations for the cognitive measures

Variables	Group						p Value
	Controls (n = 45)		PKU off diet (n = 25)		PKU on diet* (n = 25)		
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
n-back percentage accuracy							**
0-back	98.01	(1.52)	97.08	(2.46)	98.83	(1.09)	
1-back	97.13	(2.34)	95.65	(3.24)	97.78	(1.53)	
2-back	86.51	(7.95)	84.55	(7.62)	88.93	(5.69)	
n-back speed per item (s)							**
0-back	0.39	(0.04)	0.43	(0.05)	0.45	(0.08)	
1-back	0.50	(0.13)	0.60	(0.15)	0.55	(0.13)	
2-back	1.01	(0.43)	1.54	(1.17)	1.34	(0.67)	
Flanker percentage accuracy							
Compatible trials	99.28	(1.59)	98	(1.57)	99.35	(1.03)	
Incompatible trials	97.22	(2.82)	97.05	(2.28)	97.65	(3.41)	
Flanker speed per item (s)							**
Compatible trials	0.43	(0.06)	0.49	(0.07)	0.45	(0.06)	
Incompatible trials	0.46	(0.06)	0.52	(0.08)	0.47	(0.05)	
Object alternation							
10 consecutive correct trials (%)	51		28		48		
Percentage of trials correct	66.04	(16.14)	60.24	(17.75)	66.48	(15.75)	
Speed per item in s	0.76	(0.4)	0.92	(0.35)	0.88	(0.3)	
Perceptual judgement percentage accuracy							
Shape matching	98.6	(2.02)	98.2	(2.84)	99.4	(1.66)	
Function matching	98	(2.61)	97	(5.95)	97.4	(3.85)	
Perceptual judgement speed per item (s)							
Shape matching	0.82	(0.26)	0.87	(0.2)	0.99	(0.35)	
Function matching	1	(0.32)	0.98	(0.24)	1.13	(0.34)	

PKU, phenylketonuria.

*PKU on-diet group from Channon *et al.*²³

**p<0.01.

Table 4 Pearson correlations for the phenylketonuria groups between the metabolic measures and the variables that significantly differentiated the groups

Variables	n-back accuracy			n-back speed			Flanker speed	
	0	1	2	0	1	2	C	I
Off-diet PKU group								
Mean Phe level age 1–4†	–0.19	–0.12	0.13	–0.58*	–0.45	–0.14	–0.36	–0.38
Mean Phe level age 5–8†	–0.05	0.04	0.02	–0.46	–0.38	–0.30	–0.40	–0.41
Mean Phe level age 9–12†	0.16	0.44	0.24	0.01	–0.19	0.01	–0.32	–0.26
Mean Phe level age 13–16‡	0.15	0.21	–0.17	–0.14	–0.14	–0.54*	–0.10	–0.11
Mean Phe level age 17–20‡	–0.09	–0.15	–0.24	–0.04	0.09	–0.53	–0.08	–0.13
Mean Phe level age 21–24§	–0.11	–0.54	–0.26	0.37	0.28	0.07	0.35	0.28
Mean Phe level age 25–28¶	–0.10	–0.12	–0.49	0.10	0.11	–0.43	0.26	0.26
Mean Phe level age 29–32**	–0.29	–0.25	–0.22	0.33	0.38	–0.11	0.43	0.25
Concurrent Phe level‡	–0.07	–0.24	–0.24	0.55*	0.38	–0.06	0.44	0.38
Recent Phe level‡	–0.08	–0.19	–0.19	0.44	0.31	–0.14	0.41	0.32
Age of stopping diet	–0.14	–0.21	–0.21	0.33	0.38	0.28	0.24	0.19
On-diet PKU group								
Mean Phe level age 1–4††	0.29	–0.47	–0.21	0.36	–0.03	–0.39	0.24	0.27
Mean Phe level age 5–8††	0.23	–0.48	–0.11	0.55*	0.19	–0.15	0.41	0.33
Mean Phe level age 9–12††	–0.41	–0.01	0.21	0.03	0.02	0.17	–0.11	–0.13
Mean Phe level age 13–16‡	–0.17	0.13	0.39	0.09	0.13	0.10	0.15	0.08
Mean Phe level age 17–20‡	–0.15	0.18	0.34	0.10	0.13	–0.18	0.18	0.08
Mean Phe level age 21–24‡	–0.26	0.02	0.22	0.11	0.05	–0.30	0.22	0.19
Mean Phe level age 25–28‡‡	–0.36	0.20	0.59	–0.17	–0.24	–0.01	0.17	0.03
Mean Phe level age 29–32§§	–0.56	–0.04	0.32	–0.64	–0.38	–0.29	–0.59	–0.63
Concurrent Phe level‡	–0.33	–0.14	–0.07	0.22	0.26	0.23	–0.18	–0.24
Recent Phe level‡	–0.38	–0.07	–0.08	–0.37	0.06	0.08	–0.20	–0.21

PKU, phenylketonuria.

* = $p < 0.01$.† $n = 24$.‡ $n = 23$.§ $n = 22$.¶ $n = 17$.** $n = 19$.†† $n = 21$.‡‡ $n = 16$.§§ $n = 12$.

this age. Greater difficulties in maintaining dietary control in childhood may increase dietary discontinuation later, and parental factors such as social class and differing ability to control the diet may also be relevant.³ Poorer early Phe control has been associated with behavioural problems and lower IQ.³⁶ Examination of the relationships between cognitive performance and past or present Phe levels gave little support to the hypothesis that any cognitive deficits might be directly linked to dopaminergic dysfunction, although missing Phe data and the varying methods used to measure Phe over participants' lifespans may have influenced these findings. White *et al*³⁷ proposed that a combination of PFC and white matter abnormalities might account for performance deficits in PKU. We have suggested that impairments might be seen in continuously-treated PKU adults only when both dopamine depletion in PFC and underlying white matter abnormalities combine together to influence the performance.²³

Although sample sizes are relatively small, especially for the Phe level data, the overall findings are encouraging in suggesting that cognitive performance for those with PKU discontinuing diet in adolescence differs only in relatively subtle ways from either controls or those remaining on lifelong diet. Subtle cognitive deficits can nevertheless have implications for everyday performance on high-level tasks in certain circumstances. Future studies might investigate whether there are any effects on the ability to function effectively in cognitively demanding situations requiring accurate performance under time pressure (such as driving in heavy traffic, air traffic control or stock trading). With respect to the executive deficit hypothesis, the findings do not provide clear support for this, at least in adults, suggesting that other factors such as

What is already known on this topic

- Phenylketonuria (PKU) is associated with demyelination and tyrosine/dopamine deficiency, either or both of which may cause long-term clinical problems.
- Little work has been carried out examining outcomes in older populations with PKU.

What this study adds

- Neither dopamine deficiency nor demyelination alone clearly accounted for neuropsychometric outcomes; they may in combination influence performance.
- Discontinuing diet treatment in adolescence results in very subtle differences compared with controls and those with phenylketonuria remaining on diet.

white matter abnormalities may be important. Overall, our findings suggest that discontinuing diet after early and prolonged treatment does not typically lead to disastrous consequences, and may be an acceptable policy for those finding "diet for life" difficult.

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