

# Visual evoked potentials in phenylketonuria: association with brain MRI, dietary state, and IQ

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## Abstract

**At separate institutions, pattern reversal visual evoked potentials (VEPs) were recorded in children and older patients with phenylketonuria and compared with MRI of the brain. In nine patients aged less than 14 years, who were still on a diet low in phenylalanine, VEPs were clearly abnormal in only one and the abnormalities seen on MRI were mild. In 27 patients aged 14-31 years VEPs were abnormal in more than 80%, with significant reduction of amplitude and prolongation of latency despite the general absence of visual symptoms and abnormalities on routine neuro-ophthalmological examination. Among the older patients there was no significant correlation between VEP measures and plasma phenylalanine or tyrosine concentrations; neither was the incidence of VEP abnormalities dependent on whether or not the patients were still on a low phenylalanine diet. Some VEP amplitude measures were inversely correlated with the MRI lesion score, perhaps reflecting the severity of white matter abnormalities in the parieto-occipital region. In the older patients the amplitude of VEPs to stimulation of the central 8° of the visual field was significantly correlated with IQ. The study confirms the high incidence of subclinical visual pathway involvement in older children and adults with phenylketonuria, and suggests the possibility of a link between the abnormal appearance of subcortical white matter on MRI and a physiological index of function of the CNS. As there was no evidence of general intellectual decline, it is suggested that the correlation between central field VEP amplitude and IQ may reflect abnormal development during infancy. Abnormalities on MRI, on the other hand, seem to be more closely related to current dietary state and phenylalanine concentration.**

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Phenylketonuria is an inherited disorder of amino acid metabolism which results in a range of neurological problems including epilepsy and mental handicap.<sup>1,2</sup> The symp-

toms can largely be avoided by the adoption soon after birth of a diet low in phenylalanine,<sup>3</sup> although this does not completely prevent a degree of intellectual impairment. An increasing proportion of patients change to a normal or near normal diet from late childhood onwards. It has recently become apparent that this may occasionally be followed by neurological impairment, particularly of the pyramidal tracts.<sup>5,6</sup> These patients are often found to have abnormalities of the periventricular and subcortical white matter of the brain, seen on MRI.<sup>7-12</sup>

Visual evoked potentials (VEPs) are often abnormal in both untreated<sup>13,14</sup> and treated patients with phenylketonuria.<sup>15-19</sup> The locus of the abnormality has not been determined, but the common finding of prolonged VEP latencies suggests a central myelin defect causing slowing of conduction in fibres of the optic nerves or sensory radiations.

In a previous paper, the severity of MRI abnormalities in the brains of 34 patients with phenylketonuria was reported to be independently correlated with the degree of hyperphenylalaninaemia and the time elapsed since the patients had ceased taking a low phenylalanine diet.<sup>8</sup> Abnormal neurological signs such as brisk limb reflexes, tremors, or epilepsy were detected in 40% of early diagnosed cases. Abnormalities on MRI were often most conspicuous in the parieto-occipital region. In the present investigation we studied an overlapping group of 36 patients, including nine children aged less than 14, to determine what links might exist between dietary factors and physiological (VEPs), morphological (MRI), and functional (IQ) indices of CNS integrity.

## Patients and methods

Patients aged at least 7 years and attending the specialist follow up clinics at the Hospital for Sick Children and University College Hospital were approached by letter to ask if they would be willing to undergo neurological examination, MRI, and VEP studies. Of the 36 patients examined, 32 were without recent neurological symptoms<sup>8</sup> and four presented with progressive neurological deficits.<sup>6</sup> Written consent was obtained from the patients aged more than 16 years, and from the parents of the younger patients. Twenty six patients had been detected as having phenylketonuria by routine neonatal screening, nine had been diagnosed at a later date after presenting with developmental delay,

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and one had been identified by routine blood testing at the age of 5 years. The last patient had never shown any symptoms and had received no treatment. With the exception of this patient, all had received a diet low in phenylalanine until the age of at least 7 years, and had been shown to have blood phenylalanine concentrations greater than 1200  $\mu\text{mol/l}$  during a period of normal diet given after the neonatal period. Seventeen patients were still receiving regular supplements of a low phenylalanine protein substitute at the time of the study.

Details of diagnosis and follow up were obtained from the national phenylketonuria register,<sup>4,20</sup> or from the clinical notes. Results of MRI and neurological examination have been described previously.<sup>6,8</sup> Psychological assessment had been made using either WISC, or WAIS, or both (pre-1972 births) and WISC-R, or WAIS-R, or both (1972 births onwards) at 8, 14, or 18 years. The most recent intelligence quotient (IQ) was selected for each patient and adjusted to a WISC-R equivalent score as described previously.<sup>20</sup> Plasma phenylalanine and tyrosine concentrations were measured on the day of investigation with automated column chromatography (Chromakon 500, Kontron).

In nine patients aged 7.5–13.5 (mean 9.4) years, VEPs and electroretinograms (ERGs) were recorded to checkerboard reversal stimulation of both eyes separately at The Hospital for Sick Children. In 27 patients aged 14–31 (mean 21.9) years, VEPs were recorded at the National Hospital for Neurology and

Neurosurgery. The boundary age of 14 was chosen in accordance with the age range of control subjects tested in the two centres. Five silver/silver chloride disc EEG electrodes were attached in a transverse chain across the occipital region, 5 cm above the inion (less in proportion to head size in the children) and 5 cm and 10 cm to either side. Additional electrodes were attached at the inion, 2.5 cm above and 5 cm below. The reference electrode was 12 cm above the nasion. In the young children ERGs were recorded with skin surface electrodes attached to the lower eyelid with surgical tape, within 1 cm of the margin. The amplifiers' band-pass was flat from at least 3 Hz to 125 Hz and the signals were sampled at 1.67 kHz or 800 Hz for an epoch of 300 or 320 ms after each stimulus.

For the young patients a high contrast checkerboard pattern was generated on a TV monitor (Medelec Sensor system) and scalp potentials were averaged to 128 reversals at a rate of 3/s. The children either sat alone or on their parent's lap, fixating the centre of the screen which subtended 28° (horizontal) and 20° (vertical) at the eye. Each individual check subtended 50'. Responses to left and right hemifield stimulation were also recorded. The ERGs were recorded to full field pattern reversal stimulation and to diffuse flashes delivered at 3/s by a Grass PS22 stimulator (setting 4) placed 25 cm from the eye.

For the older patients the checkerboard was back projected on to a centrally fixated,

Table 1 Patient data (patients younger and older than 14 years were tested in different centres and were therefore analysed separately)

No	Sex	Age (y)	IQ	Phe ( $\mu\text{mol/l}$ )	Tyr ( $\mu\text{mol/l}$ )	Diet start (days)	MRI score	VEP
1	F	7.5	106	649	74	13†	1	N
2	F	7.5	101	348	107	10†	1	N
3	F	8	114	571	112	5†	1	N
4	F	8.5	118	722	29	28†	1	N
5	F	8.8	90	915	30	11†	1	N
6	M	9.2	114	1166	23	11†	3	N
7	F	11	119	642	73	28†	1	N
8	M	11	74	1320	34	13†	4	Abn (LH del)
9	M	13.5	115	1035	27	14†	2	N
10	M	14	102	1174	41	—	2	N
11	M	16	113	1283	75	11†	3	Abn (del, RELH att)
12	F	16	85	1639	57	14†	3	Abn (del)
13	M	17	67	707	101	13†	1	Abn (del, LERH att)
14	M	17	80	1611	35	19	3	N
15	F	18	70	1718	75	13	4	Abn (RE del, LERH att)
16	M	18	77	1580	17	16†	3	Abn (del, C att)
17	M	19	127	1735	41	18	2	N
18	M	19	99	1410	28	28	5	Abn (C + RH del, RE att)
19	M	20	105	1569	41	28	4	Abn (RH del, RERH att)
20	M	21	114	1364	36	50	4	Abn (del)
21	M	22	77	1154	65	16†	2	Abn (del, RELH att)
22	M	22	114	1186	25	43†	2	Abn (C + LEF del, LEC att)
23	M	22	44	959	41	372†	4	Abn (del)
24	M	23	106	1333	27	895	3	N
25	F	23	79	430	179	244	4	N
26	M	24	49	—	—	497	5	Abn (att)
27	M	24	—	—	—	5†	5	Abn (del, C att)
28	M	24	65	1258	57	44	5	Abn (del, RH + C att)
29	F	24	93	1635	37	5	4	Abn (RH del)
30	F	25	97	1208	73	61	4	Abn (REF + RELH del)
31	M	25	82	2010	46	730	2	Abn (del)
32	F	25	44	1814	31	400	3	Abn (del)
33	F	26	68	1157	26	1030	3	Abn (REC del)
34	M	27	97	—	—	410	2	Abn (del, REC att)
35	F	29	82	883	53	10	3	Abn (C + RELH del, RERH att)
36	F	31	—	1364	34	497	3	Abn (del, RH del)

†Still on low phenylalanine diet; Phe = phenylalanine; Tyr = tyrosine; LE = left eye; RE = right eye; F = full field; C = central field; LH = left half field; RH = right half field; N = normal; Abn = abnormal; del = delayed; att = attenuated.

Table 2 VEP amplitude and latency to full field stimulation of either eye in the 27 older patients with phenylketonuria and 27 age matched controls, compared by Student's *t* test (unpaired, two-tailed probabilities)

	Left eye		Right eye	
	Amplitude ( $\mu$ V)	Latency (ms)	Amplitude ( $\mu$ V)	Latency (ms)
Patients:				
Mean	9.7	116.0	8.8	115.5
SD	3.9	6.1	3.6	6.1
Controls:				
Mean	13.8	104.7	12.9	104.7
SD	4.5	4.2	5.2	4.4
P value	< 0.001	< 0.001	< 0.01	< 0.001

circular screen subtending  $32^\circ$  (each check subtending  $50'$  and 200 responses were averaged at a rate of 2/s by methods previously described.<sup>21</sup> In all the older patients except one, who was unable to cooperate for the necessary period, responses were also recorded to stimulation of the left and right hemifields and a circular central field subtending  $8^\circ$ .

Magnetic resonance imaging was performed with a Picker-Vista 0.5 Tesla scanner

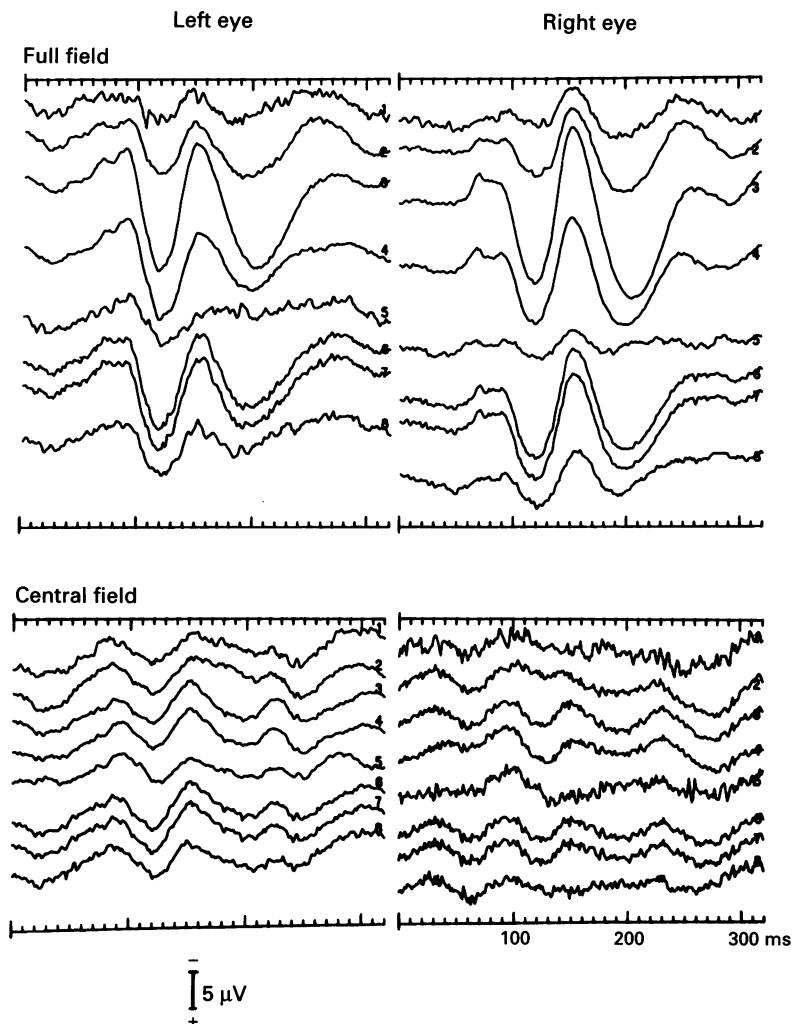


Figure 1 Full field VEPs of large amplitude but slightly prolonged latency from both eyes in patient 16. The latency of the P100 peak in channel 3 was 120 ms on the left and 119 ms on the right (normal mean 105 ms, + 2.5 SD limit 116 ms). The central field responses were also delayed and abnormally small (< 20%) in comparison with the full field amplitudes, suggesting a relative defect of fibres serving macular vision although visual acuity was normal and no abnormalities were detected on routine neuro-ophthalmological examination. Electrodes 1-5 were in a lateral chain (L-R) 5 cm above theinion, separation 5 cm, with electrode 3 on the midline. Electrodes 6-8 were on the midline 2.5 cm above, at and 5 cm below theinion. The reference electrode was 12 cm above the nasion.

with T2 weighted sequences (SE 2000/60) and 24 contiguous slices with a  $128 \times 256$  image matrix. Scans were reported by a neuroradiologist (BK) who was unaware of the VEP and clinical findings. Scans were graded 0 if considered normal or equivocal, 1-5 if abnormal in proportion to the severity of white matter changes.<sup>8</sup>

The VEPs were classified as abnormal when the P100 latency (or the interocular or interhemifield latency difference) was more than 2.5 SD above the mean of the appropriate control group, or when the P100 amplitude (or the interocular, interhemifield or central/full field amplitude ratio) was more than 2.5 SD below the control mean. Amplitude values were first converted to logarithms to normalise their distribution. For comparison of continuous variables (VEP amplitude and latency measures, blood phenylalanine and tyrosine concentrations, age, IQ) *t* tests and Pearson correlation coefficients (*r*) were used. For comparison of VEP values with categorical data (MRI lesion score), Pearson's rank correlation coefficient (*r<sub>s</sub>*) was calculated. The correlation between abnormalities in different measures was assessed by calculating  $\chi^2$  for a  $2 \times 2$  contingency table.

## Results

### YOUNG PATIENTS

All the patients aged 7-14 years were on a low phenylalanine diet which had commenced before the age of 1 month (table 1). The VEPs were within normal amplitude and latency limits without significant interocular or interhemifield asymmetry in eight of nine patients. In the other (patient 8) the latency of the full field response to right eye stimulation was at the upper limit of normal and hemifield responses were abnormally delayed for left half field stimulation of both eyes ("uncrossed" asymmetry<sup>22</sup>), suggesting the possibility of retrochiasmal visual pathway involvement in the right hemisphere. In intergroup comparison, the responses of the patients did not differ significantly from those of age matched controls. The ERGs to pattern reversal and flash stimulation were normal in every case. Magnetic resonance imaging was considered abnormal in every case, although in six the abnormalities were mild (grade 1). The patient with abnormal VEPs had the most pronounced MRI abnormalities (grade 4) but without any notable asymmetry between the left and the right hemispheres, which might account for the VEP asymmetry. No abnormalities were detected on neurological or neuro-ophthalmological examination, but the patient with abnormal VEPs and grade 4 MRI abnormalities had by far the lowest IQ score (74 compared with 90-119).

### OLDER PATIENTS

Out of 27 patients aged 14-31 years, VEPs were abnormal in 22 including four who had presented with neurological deterioration

(81%, table 1). On average, VEP latencies were prolonged by approximately 10 ms compared with age matched controls ( $P < 0.001$ , table 2) and amplitudes were reduced by about 40% ( $P < 0.01$ ). Abnormally prolonged latencies were recorded in 21 patients, affecting the responses of both eyes in 18 (figs 1 and 2 give examples) and of one eye in three. Latency asymmetries between left and right hemifield VEPs of both eyes ("uncrossed" asymmetry<sup>22</sup>) suggested the possibility of retrochiasmal visual pathway involvement in three cases (18, 29, 36). Amplitudes of VEPs were abnormally low in 14 cases, affecting the responses of both eyes in three and of one eye in 11 patients. An uncrossed amplitude asymmetry was seen in patient 29.

#### Correlation with ocular examination

In 23 of the older patients the corrected visual acuity was assessed with a Snellen chart at a distance of 6 m. Acuity was 6/9 or worse in one or both eyes of nine patients (total 15 eyes). There was no significant tendency for VEP latencies to be longer or amplitudes lower in the eyes with diminished visual acuity. Examination of the pupillary reflexes, fundi, and visual fields was normal in every case.

#### Correlation with MRI

In the patients aged 14 and older, VEPs were

abnormal in one of one with score 1, four of six (67%) with score 2, six of nine (67%) with score 3, six of seven (86%) with score 4, and four of four (100%) with score 5. There was a significant correlation between VEP amplitude and lesion score for the full field responses of the right eye ( $r_s = -0.45$ ,  $P = 0.04$ ) and the left hemifield responses of the left eye ( $r_s = -0.49$ ,  $P = 0.02$ ). This was mainly due to responses of very low amplitude being recorded in the four patients with a lesion score of 5, and no significant correlation with lesion score was detected for six other amplitude measures. The VEP latencies showed no significant correlation with lesion score. In the three cases for whom uncrossed VEP asymmetries suggested the possibility of retrochiasmal visual pathway involvement, MRI did not disclose any notable asymmetry of signal in the occipital lobes and white matter.

#### Correlation with phenylalanine and tyrosine concentrations

In the patient group as a whole ( $n = 36$ ) there was a marginal tendency for abnormal VEPs to be associated with higher phenylalanine concentrations; only three of 17 patients with phenylalanine  $> 1200 \mu\text{mol/l}$  had normal VEPs, whereas 10/16 with lower phenylalanine concentrations had normal responses ( $\chi^2 = 5.194$ ,  $P < 0.05$ ). Among the 27 older patients, for whom the VEP data was homogeneous, VEP amplitudes to full field stimulation of the right eye showed a marginally significant inverse correlation with plasma phenylalanine concentrations ( $r = -0.407$ ,  $P < 0.05$ ) but there were no other significant correlations with phenylalanine or tyrosine.

#### Correlation with dietary control

Abnormal VEPs were recorded in eight of eight older patients who were still on a controlled diet at the time of testing, compared with 14 of 19 who had changed to a normal or near normal diet ( $\chi^2$  NS). The VEPs were abnormal in 15 of 17 older patients whose treatment commenced shortly (mean 23 days) after birth, compared with seven of 10 whose diet was not started until the age of 8 months or more ( $\chi^2$  NS). Among the 17 older patients who commenced treatment at an early age there was a difference approaching significance ( $t = 2.09$ ,  $P < 0.1$ ) between the VEP latencies of seven who were still on a low phenylalanine diet at the time of the study and 10 who had changed to a normal diet; however, the VEP latencies were on average slightly longer in the controlled diet group, suggesting that this could have been a chance finding.

#### Correlation with IQ

Among the older patients with homogeneous VEP data a significant correlation was found between VEP amplitudes and IQ. Left and right eye responses showed significant correlations for both the full and central fields ( $r = 0.467$  to  $0.593$ ,  $P < 0.05$  to  $0.01$ ) and the correlation was also significant for the right

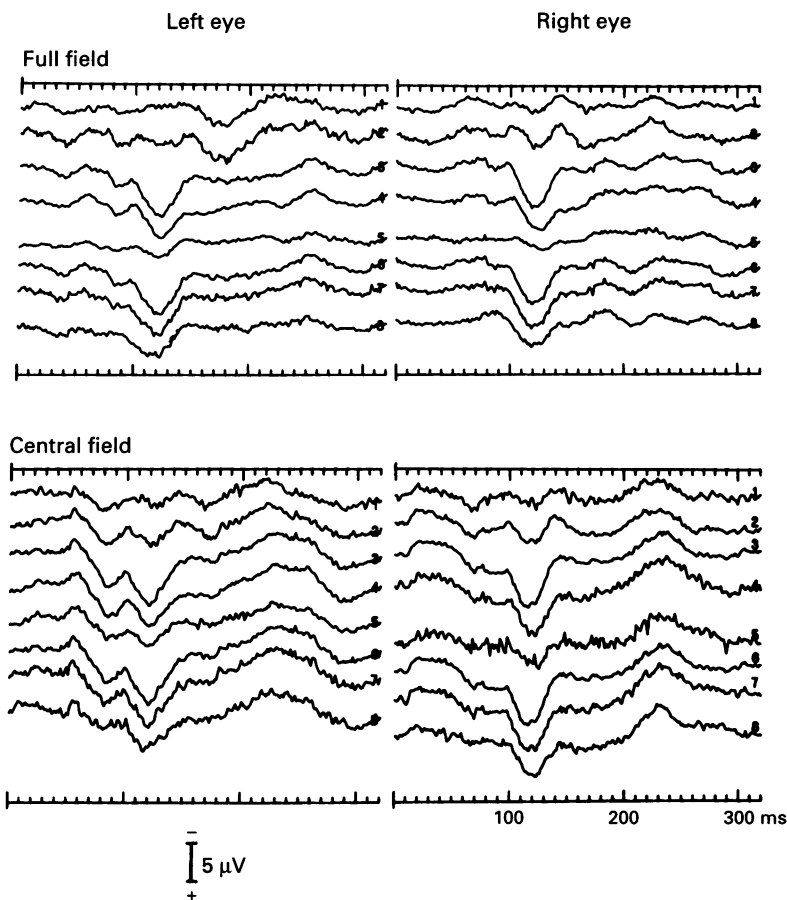


Figure 2 VEPs of low amplitude and slightly prolonged latency in patient 21. In this patient the full and central field responses were similar in amplitude. Visual acuity was normal and no abnormalities were detected on neuro-ophthalmological examination. Electrode locations were as in fig 1

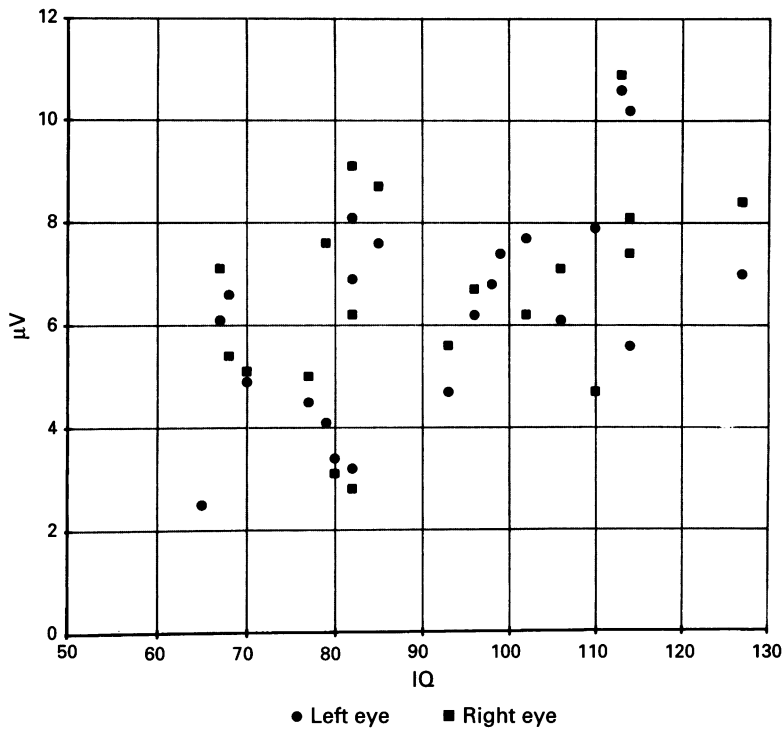


Figure 3 Scattergram of central field VEP amplitudes against IQ among the older patients, excluding those with very low IQ, amblyopia, or doubtful fixation/alertness. Left eye  $r = 0.582$   $P < 0.01$ , right eye  $r = 0.543$   $P < 0.02$

hemifield response of the left eye ( $r = 0.625$ ,  $P < 0.001$ ). There was a marginally significant negative correlation between IQ and VEP latency for the full field responses (left eye  $r = -0.355$   $P < 0.1$ ; right eye  $r = -0.409$   $P < 0.05$ ). In view of the possibility that the patients of low IQ may not have fixated the stimulus screen consistently, the correlation was recalculated excluding three patients with IQ less than 50, the right eye responses of one patient with amblyopia, and the central field responses of two eyes in which there was doubt over the patient's fixation or alertness. Among the remainder, the central field responses amplitudes were still significantly correlated with IQ (left eye  $r = 0.582$   $P < 0.01$ , right eye  $r = 0.543$   $P < 0.02$ , fig 3). Among the 34 patients of the overall group in whom a recent IQ score was available, this was inversely correlated with the patient's age at the time of the VEP recording ( $r = -0.454$   $P < 0.01$ ). Among the 25 older patients IQ was not significantly correlated with age ( $r = -1.319$   $0.1 < P < 0.2$ ). There was no significant correlation between IQ and plasma phenylalanine or tyrosine concentrations.

### Discussion

To consider previous VEP studies in order of the patients' ages, Cardona *et al* examined eight early treated cases at various times during the first 12 months.<sup>19</sup> Flash VEPs were delayed in 15 records out of 31; only one patient was within normal limits on each occasion but no patient was abnormal in every test. Abnormalities were not related to phenylalanine concentrations, nor to the patient's age at the time of onset of diet or the achieve-

ment of successful dietary control. A similar incidence of six of 14 abnormal records was reported by Landi *et al* for treated patients aged 5–16 years.<sup>16</sup> The abnormalities were all among patients with relatively high phenylalanine concentrations ( $< 10$  mg/100 ml) over the preceding year, and five of six were from patients whose dietary control commenced after the age of 2 months. The lower incidence of abnormalities among patients of the present study up to the age of 16 years may be explained by the fact that at the time of testing only six (including the three with abnormal VEPs) had a phenylalanine level above 1000  $\mu\text{mol/l}$  (equivalent to 16.7 mg/100 ml) and all except one (with normal VEPs) commenced their diet before one month of age.

Among 25 early treated patients with classic (type 1) or mild (type 2) phenylketonuria, tested at a mean age of about 16 years, Korinthenberg *et al* found the VEP latency to be significantly correlated with the mean phenylalanine concentration during the first decade of life but not with subsequent measures.<sup>18</sup> After controlling for the effect of phenylalanine concentration during the first 10 years, there was no significant difference in mean VEP latency according to whether the diet had been discontinued before or after this age, or not at all.

Shafer and McKean recorded VEPs in four untreated patients aged 17–18 years.<sup>13</sup> A shortening of latency was found after phenylalanine concentrations had been reduced to less than 6 mg/100 ml by dietary control. Treatment with amino acid precursors had a similar effect, although not when given singly. Among the six untreated adults studied by Creel and Buehler,<sup>14</sup> prolonged VEP latencies were recorded in four. Interestingly, the magnitude of VEP delays in this series was no greater than that of the treated patients in the present study.

Our study confirms previous reports that VEP abnormalities are frequent even among early diagnosed cases. The electrophysiological abnormalities were correlated, albeit weakly, with the MRI lesion score, suggesting that it may be a myelin defect in the subcortical white matter which is responsible for the decreased VEP amplitude and prolonged latency. However, as there was no direct evidence of a link between subcortical white matter involvement and VEP abnormalities (such as might have been provided by an uncrossed VEP asymmetry in a patient with correspondingly asymmetric occipital MRI signal), it is possible that the VEP abnormalities may have been due to defects elsewhere in the visual pathway - for example, the optic nerves.

One of the most striking findings was the apparently abrupt increase in the incidence of VEP abnormalities in the patient group aged 14 and older, coinciding with a tendency for the diet to be relaxed and for MRI abnormalities to become more pronounced. It did not seem to be an important factor that some of the older patients commenced their diet relatively late, but with few such patients in the

study this possibility cannot be excluded. The incidence of VEP abnormalities was weakly associated with that of plasma phenylalanine concentrations above 1200  $\mu\text{mol/l}$ , but no correlation could be established between phenylalanine concentrations and parametric VEP measures. It must be stressed that the younger patients of the present study were recorded in a different centre with slightly different methods, and their test may have been less sensitive on account of the greater difficulty young subjects have in maintaining concentration on the stimulus screen.

A second notable finding was a significant correlation between central field VEP amplitudes and the patients' IQ, after taking measures to try to ensure that this was not a trivial consequence of poor attention to the stimulus. No correlation between VEP amplitude and IQ has been shown for normal subjects, and IQ in patients with phenylketonuria is rather stable throughout the later years of childhood and early adulthood (the correlation of IQ with age was non-significant for the patients aged 14 and older). Therefore it is argued that the reduction in central field VEP amplitude may reflect events occurring during early development which also determine intellectual state in later life. The abnormal VEPs could signal a dysfunction of the subcortical white matter which is also reflected by the changes seen in MRI, but the latter were not found to be significantly correlated with IQ<sup>8</sup> and were more strongly associated with current phenylalanine concentrations.

It is concluded that VEPs disclose a high incidence of abnormalities in adult patients with phenylketonuria, correlating to a small degree with the severity of brain tissue changes seen in MRI and plasma phenylalanine concentrations but more strongly with intellectual performance. By contrast with MRI changes, which are to some extent associated with current phenylalanine concentrations, the VEP abnormalities seem to be more closely linked with earlier events which may also be involved in the determination of IQ. Although VEPs may prove to be relatively insensitive to late onset neurological deterioration, the high incidence of abnormalities among early diagnosed patients irrespective of their dietary history re-emphasises the need for further studies on the relation between early diet and long term neurological integrity.

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