Wechsler subscale IQ and subtest profile in early treated phenylketonuria

P V Griffiths, C Demellweek, N Fay, P H Robinson, D C Davidson

Abstract

Aim—Mildly depressed IQ is common in treated phenylketonuria. This study explored whether a particular intellectual ability profile typifies early and continuously treated phenylketonuria and whether component skills comprising the IQ relate to socioeconomic and treatment factors.

Methods—IQ scores were collected retrospectively from variants of the “Wechsler intelligence scale for children” performed at age 8 on 57 children with early treated, classic phenylketonuria. The mental ability pattern underlying IQ was investigated by analysing subscale and subtest scores and dietary factors, such as historical phynylalanine blood concentrations.

Results—The children’s mean full scale IQ of 91.11 was significantly below the healthy population norm. There was a significant discrepancy between their mean verbal IQ (94.65) and mean performance IQ (89.42), suggestive of a spatial deficit, but the data did not support a biochemical or sociological explanation. Individual Wechsler subtests had no distinctive pattern. Phynylalanine control at age 2 was predictive of overall IQ. At this age, children with annual median phynylalanine < 360 μmol/litre (recommended UK upper limit) had a mean IQ 10 points higher than those above.

Conclusions—Early and continuous treatment of phenylketonuria does not necessarily lead to normalisation of overall IQ. Verbal intelligence in the primary school years appears to normalise if blood phynylalanine is maintained below 360 μmol/litre in infancy, but spatial intelligence may remain poor. However, the discrepancy in skill development is not the result of social status or treatment variables. Perhaps weak spatial intelligence is an ancillary effect of a protective rearing style occasioned by the dietary treatment regimen.

Keywords: phenylketonuria; intelligence quotient; dietary treatment; policy

Since the initiation in the 1960s of mass screening for phenylketonuria (McKusick 261600), treatment outcome during the school age period has been assessed principally by the “Wechsler intelligence scale for children” (WISC). In general, outcome studies have related Wechsler IQ to independent variables such as severity, age of commencement of dietary phynylalanine restriction, phynylalanine range during treatment, and age of dietary discontinuation. Most studies have selected the overall or full scale IQ as the dependent variable, this paradigm typifying the approach taken by national collaborative studies in the UK and the USA. Although the full scale IQ provides a convenient summary of intellectual development, it obscures the richness of information about individual or group profiles of mental skill inherent in WISC assessments. To our knowledge, among studies of treatment factors in phenylketonuria, there are no reports concerning the 10 subtest scores on which full scale and subscale IQs are based, despite their necessarily having been collected in the course of testing. Thus, the question of whether a particular WISC subtest profile characterises treated phenylketonuria has not been explored.

Verbal and performance IQ subscale scores on the WISC have been reported occasionally and the findings of higher verbal than performance IQ scores suggest that visuospatial cognitive functioning might be poorer than verbal linguistic abilities. A more frequently documented finding is that full scale IQ falls below that of siblings, parents, and the population norm. In relation to the verbal to performance IQ discrepancy and Wechsler profile issue, this begs the question whether lowered IQ is the result of uniform depression of subtest scores or whether specific cognitive skills contribute more than others to the deficiency. A further reason for exploring the Wechsler profile is to appraise whether the mild hyperphenylalaninaemia typical of the treated condition might be responsible for imbalances in cognitive development. The history of phenylketonuria research is punctuated with reports suggesting that specific skill deficits might accompany treatment conducted according to the standards of the day; however, despite the WISC being the most common measure of cognition during and after dietary treatment, it is a paradox that the WISC subtest profile has not been examined for strengths and weaknesses and how these might reflect dietary phynylalanine control.

The aim of our study was to fill this gap in the knowledge base by retrospectively gathering data from Wechsler tests given to treated children with phenylketonuria and analysing scores not only at the overall IQ level but also at the subscale (verbal and performance IQs) and subtest levels. Five verbal linguistic subtests underlie the verbal IQ. With the psychological constructs they measure in brackets, they are:
information (factual knowledge), similarities (verbal concept formation), arithmetic (mental arithmetic), vocabulary (word definitions), and comprehension (social understanding). Five visuospatial subtests underlie the performance IQ: picture completion (perception of visual detail), picture arrangement (logical reasoning), block design (visual analysis), object assembly (part/whole construction), and coding (symbol manipulation).

The patient sample for our study was compiled to represent the phenylketonuria population currently of paramount clinical interest; namely, the early and continuously treated classic group. Although in all cases treatment had been continuous until the time of testing at 8 years of age, lifetime control of dietary phenylalanine intake varied, thereby allowing investigation of associations between historical phenylalanine concentrations and WISC scores. Furthermore, pretest phenylalanine control could be categorised in terms of its conformity to current UK guidelines, thus enabling the exploration of treatment compliance effects on Wechsler profiles.

Methods

PATIENT SAMPLE

The sample consisted of 57 children (27 boys and 30 girls), 32 of whom were derived from the Liverpool phenylketonuria register and 25 from the Glasgow phenylketonuria register. Only data from children with classic or type 1 phenylketonuria and in whom dietary restriction of phenylalanine began before the 8th week of life were entered into the analysis. Classic phenylketonuria was operationally defined as peak phenylalanine concentrations in blood greater than 1200 µmol/litre before treatment. Data from children with known neurological or psychiatric comorbidity were excluded. When tested for IQ, each child was as near as possible to his or her 8th birthday, the mean chronological age at test of the sample being 8.14 years (SD, 0.30).

IQ TESTS

In each case, the most recent revision of the WISC current at the time of testing was used to measure IQ. Four variants were administered: the original WISC, the “Wechsler intelligence scale for children revised” (WISC-R), the “Wechsler intelligence scale for children revised, Scottish edition” (WISC-RS), and the “Wechsler intelligence scale for children third UK edition” (WISC-3UK). Eleven children received the WISC, 32 the WISC-R, one the WISC-RS, and 13 the WISC-3UK. Full scale, verbal, and performance IQs, and subtest scaled scores were collated.

DESIGN, PROCEDURE, AND ANALYSIS

Our study was a retrospective analysis of IQ outcome in relation to treatment factors and social class. Testing was conducted close to the children’s 8th birthdays, this timing complying with that required of regional centres by the protocol of the UK national collaborative study of phenylketonuria. Tests were administered by clinical and educational psychologists between the years 1972 and 1998 (median, 1986). Independent variables were peak pre-treatment phenylalanine concentration (the highest diagnostic reading in µmol/litre), age treatment started (in days postpartum), and indices of dietary control, these being annual median phenylalanine concentrations (µmol/litre) during the first 8 years of life. Social class, operationally defined in terms of the income of the chief earner in the family, was also included as an independent variable and measured on a scale of 1 to 7, with 1 representing professional employment and 7 unemployment. Dependent variables were WISC full scale IQ, verbal subscale IQ, performance subscale IQ, and subtest scaled scores. Results from the various revisions of the WISC are standardised on age stratified child populations, thereby permitting norm referenced comparisons. Full scale IQ was corrected for upward drift in population norms over time, using the method described by Smith et al.

Regression analyses were performed on within group associations between treatment factors and IQs at age 8. As a test of the UK recommendation for dietary treatment that blood phenylalanine concentrations be kept below 360 µmol/litre in the preschool years, the sample was divided into two groups according to whether individual control in the 2nd year of life was above or below the cut off point of 360 µmol/litre. The age at which the sample was split was determined by stepwise dropout regression. The dataset was analysed by MiniTab version 10.5 (statistical package for the Macintosh computer). Standard deviations and mean values are given, two tailed tests were used throughout, and α was set at 0.05 or less.

Results

TREATMENT VARIABLES AND SOCIAL CLASS

Peak diagnostic phenylalanine concentrations in the 57 children before treatment ranged from 1200 to 5400 µmol/litre (mean, 2557; SD, 1047) and the day of life that treatment began ranged from 4 to 55 (mean, 17.15; SD, 8.94). Yearly indices of dietary control (IDCs) for individual children until age 8 were averaged across the group. Figure 1 shows the resulting curve. One way analysis of variance (ANOVA) confirmed the significance of the rise in mean IDC with increasing age (F = 4.27; degrees of freedom (df), 7/448; p < 0.001). Average lifetime phenylalanine as measured by the mean annual IDC was 466 µmol/litre (SD, 154). Mean social class on the seven point scale was 4.56 (SD, 1.56).

IQ OUTCOME AND POPULATION NORMS

Full scale, verbal, and performance IQ scores were all normally distributed (Anderson-Darling test). The uncorrected mean full scale IQ was 91.11 (SD, 14.01), the verbal IQ mean was 94.65 (SD, 13.99), and the performance IQ mean was 89.42 (SD, 14.69). The discrepancy between the verbal and performance IQs was significant (t = 3.25; df, 56; p < 0.01, related). The uncorrected mean full scale IQ...
IQ test profile in phenylketonuria

Table 1 Subgroup variable scores for low and high phenylalanine groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Peak phenylalanine (µmol/l)</th>
<th>Start day</th>
<th>Social class (1–7)</th>
<th>cFSIQ</th>
<th>FSIQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low phenylalanine</td>
<td>(n = 29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.12 (0.3)</td>
<td>2311 (1070)</td>
<td>17.8 (11.3)</td>
<td>4.41 (1.62)</td>
<td>90.6* (12.2)</td>
<td>95.07** (13.47)</td>
<td></td>
</tr>
<tr>
<td>High phenylalanine</td>
<td>(n = 28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.16 (0.3)</td>
<td>2811 (977)</td>
<td>16.5 (5.7)</td>
<td>4.71 (5.1)</td>
<td>80.8* (14.0)</td>
<td>87.00** (13.58)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean (SD).

The low phenylalanine group (individual indices of dietary control (IDCs) < 360 µmol/litre at age 2) and the high phenylalanine group (individual IDCs > 360 µmol/litre at age 2) were matched for age at test, peak pretreatment phenylalanine, day of treatment commencement, and social class, but differed significantly in both corrected full scale IQ (cFSIQ) and uncorrected FSIQ.

*p < 0.01; **p < 0.005.

was significantly below the population norm (Z = −4.48; p < 0.001), as was the mean verbal IQ (Z = −2.69; p < 0.01) and the mean performance IQ (Z = −5.33; p < 0.001). After correcting the WISC and WISC-R scores for temporal drift in population norms, the mean full scale IQ fell to 85.82 (SD, 13.93). The difference between the uncorrected and corrected full scale IQ figures was significant (t = 12.29; df, 56; p < 0.001, related).

TREATMENT FACTORS, SOCIAL CLASS, AND FULL SCALE IQ

In view of the significant difference between the uncorrected and corrected full scale IQ distributions, the corrected full scale IQ was used as the central outcome variable. When the corrected full scale IQ was regressed on peak phenylalanine before treatment, day of treatment commencement, mean lifetime phenylalanine, and social class, the latter combination was found to predict IQ outcome reliably (F = 4.65; df, 4/52; p < 0.01). However, stepwise regression revealed that only the IDC distribution at year 2 remained as consistently having a significant influence on later IQ. With social class controlled, partial correlation revealed that phenylalanine concentrations at year 2 remained significantly predictive of corrected full scale IQ (Z = −2.18; p < 0.05).

TREATMENT POLICY AND FULL SCALE IQ

In the light of the finding that the association between corrected full scale IQ and lifetime phenylalanine control was principally the result of variance in blood phenylalanine in the 2nd year of life, the sample was divided according to whether individual children’s concentrations fell above or below 360 µmol/litre at this age, 360 µmol/litre being the upper limit of the treatment target range currently recommended in the UK for the preschool period. This procedure yielded two subgroups for comparison of IQ, one containing 29 children whose individual IDCs at year 2 were less than 360 µmol/litre, and one containing 28 children whose IDCs were above. The average phenylalanine concentrations for the low and high phenylalanine group were 287 (SD, 66) and 539 (SD, 127) µmol/litre, respectively. Because their phenylalanine distributions did not overlap, this difference was significant (t = 9.32; df, 55; p < 0.001, unrelated). Furthermore, only the phenylalanine concentrations differentiated the groups who were otherwise matched on chronological age (t = 0.43), peak pretreatment phenylalanine (t = 1.84), day of starting treatment (t = 0.55), and social class (t = 0.73) (all t ratios: df, 55; p not significant (NS) (table 1).

The mean corrected full scale IQ of the low phenylalanine group was 10 points higher than that of the high phenylalanine group (table 1), this difference being significant (t = 2.81; df, 55; p < 0.01). Likewise, when uncorrected full

![Figure 1: Yearly averages in µmol/litre of median phenylalanine concentrations between ages 1 and 8 for entire sample (n = 57).](http://adc.bmj.com/)

Figure 1: Yearly averages in µmol/litre of median phenylalanine concentrations between ages 1 and 8 for entire sample (n = 57).
scale IQs were analysed, the low phenylalanine group remained superior (t = 2.25; df, 55; p < 0.05).

TREATMENT POLICY AND SUBSCALE IQ
Table 2 shows verbal and performance IQ scores for the low and high phenylalanine groups. As can be seen, the mean verbal IQ for the low phenylalanine group was normal. Mixed design ANOVA of verbal and performance IQ scores between the low and high phenylalanine groups revealed significant main effects for phenylalanine control (F = 5.87; df, 1/55; p < 0.05) and subscale (F = 10.92; df, 1/55; p < 0.01) and a significant interaction (F = 4.29; df, 1/55; p < 0.05). Post hoc paired mean comparisons (Scheffe) confirmed that the difference between the verbal and performance IQs of the low phenylalanine group was significant (p < 0.05) and that the verbal IQ of the low phenylalanine group was significantly above that of the high phenylalanine group. Other comparisons were non-significant. When the verbal to performance IQ difference within the low and high phenylalanine groups was regressed separately on severity (peak phenylalanine), treatment factors (start day, IDC at year 2, and lifetime phenylalanine), and social class, no significant associations emerged.

SUBSCALE IQ, SEX, SOCIAL CLASS, AND TREATMENT FACTORS
Although the discrepancy for the entire sample between the verbal IQ mean of 94.65 and the performance IQ mean of 89.42 was significant (F = 10.74; df, 1/55; p < 0.01), sex effects were absent. The 27 boys had mean verbal and performance IQ scores of 95.11 (SD, 15.61) and 88.48 (SD, 15.03), respectively; the 30 girls had mean verbal and performance IQ scores of 94.23 (SD, 12.61) and 90.27 (SD, 14.58), respectively. However, neither the sex factor (F = 0.017; df, 1/55; p, NS) nor the interaction between sex and subscale was significant (F = 0.68; df, 1/55; p, NS). To assess whether the verbal and performance IQ imbalance in cognition could be attributed to social class or treatment factors, individual verbal to performance IQ differences for all children were regressed on social class, peak phenylalanine, start day, and mean lifetime phenylalanine. Neither the multiple regression equation nor any of the individual factors were found to be significantly predictive, suggesting that the inconsistency in the subscales of the Wechsler tests was associated with characteristics other than treatment history and social background. This view was confirmed by simple correlation and stepwise dropout regression using annual mean IDCs as predictors. Verbal IQ correlated negatively and significantly with preschool phenylalanine (r = −0.29; df, 55; p < 0.05), but performance IQ was not associated with phenylalanine at any age.

SUBTEST PROFILE
Figure 2 shows the profile of the individual subtest means of the Wechsler tests. These are age corrected and standardised on a scale with a population mean of 10 and a standard deviation of 3. The supplementary “digit span” and “mazes” subtests were not routinely administered and hence do not appear. Despite the mean verbal and performance IQs being significantly inferior to the population norm, not all the subtests echoed this pattern. Z tests for sample to population comparisons showed the following subtest means to be significantly below the population average:
- information (Z = −4.15; p < 0.001)
- picture completion (Z = −3.10; p < 0.01)
- picture arrangement (Z = −3.98; p < 0.001)
- object assembly (Z = −3.05; p < 0.01)
- coding (Z = −4.58; p < 0.001)

The remaining subtests—similarities, arithmetic, vocabulary, and comprehension—did not differ significantly from age expectations. Thus, all the performance scale subtests fell significantly below the population norm, but among the verbal scale subtests only information was significantly depressed. Multiple and stepwise regression analysis failed to show any significant associations between treatment factors and individual subtests except for information, which was predicted by IDC at year 2 (F = 10.41; df, 1/55; p < 0.01).

PHENYLALANINE CONTROL AND HISTORICAL TREATMENT PERIOD
Because the sample comprised patients treated over a long period in the history of phenylketonuria, the question of whether phenylalanine control in the 1960s and 1970s might have been less strict than in the 1980s was
investigated empirically. Although the lifetime phenylalanine mean of 500 µmol/litre (SD, 144) for the 28 patients first treated between 1964 and 1977 was higher than that of 433 µmol/litre (SD, 159) for the 29 patients first treated between 1978 and 1990, the difference was not significant (t = 1.67; df, 55; p, NS).

Discussion
In summary, the principal findings were:
- phenylalanine control worsened progressively with age
- no evidence was found for more stringent phenylalanine control in the 1980s than in the 1970s
- average full scale IQ fell significantly short of age expectation, irrespective of correction for normative drift over time
- sex had no effect on overall or subscale IQ
- social class correlated significantly with lifetime phenylalanine and full scale IQ
- when social class effects were controlled, lifetime phenylalanine, and especially phenylalanine concentrations at age 2, predicted full scale IQ
- children with average phenylalanine concentrations below 360 µmol/litre at age 2 achieved a mean full scale IQ 10 points higher at age 8 than those with phenylalanine concentrations above 360 µmol/litre at the same age
- verbal IQ was significantly superior to performance IQ but the discrepancy was not accounted for by historical phenylalanine concentrations
- early phenylalanine control below 360 µmol/litre was associated with normal verbal IQ but significantly depressed performance IQ
- compared with population standards, the Wechsler subtest profile was characterised by abnormally low scores on all performance subscale measures, whereas the verbal subscale measures, with the exception of information, were within normal limits.

Rigid inclusion criteria ensured the sample tested was uncontaminated by variables such as lateness of treatment or mild hyperphenylalaninaemia. Thus, there is no reason to believe that the children tested were unrepresentative of the wider early treated, classic phenylketonuria population at age 8 and that the above results suffer from sample bias.

Between birth and age 8, loss of phenylalanine control was incremental and relentless (fig 1), mean IDCs mirroring those reported by Weglage et al for a similar early treated group.23 Year by year increases in phenylalanine concentrations in treated phenylketonuria have been reported elsewhere; however, the notion that clinical practice has become more stringent over the course of the past 25 years was not supported by the dataset.

The finding that phenylalanine control at age 2 was the most powerful predictor of later IQ adds weight to the view that phenylalanine affects IQ most adversely in the early years of life and emphasises the importance of good dietary control in infancy. Independent national studies have concluded that phenylalanine only affects IQ until age 5,24-25 the implication being that the influence of raised phenylalanine concentrations diminishes over the preschool period. In support of this theory, for the sample as a whole, mean phenylalanine between birth and age 5 correlated significantly and negatively with uncorrected full scale IQ at age 8 (r = −0.26; df, 55; p < 0.05), whereas the association between mean phenylalanine from age 6 to 8 and full scale IQ was random. This pattern also obtained for corrected full scale IQ.

We found the mean uncorrected full scale IQ to be 91.11, which agrees with earlier26 and more recent findings,27 and is not only significantly below the norm for the healthy population but is also below the figure of 94 for a sample of 14 year old treated patients.28 However, although there is converging evidence that full scale IQ in early treated phenylketonuria falls below age standards, the data in table 1 confirm that maintaining phenylalanine below the upper limit recommended in the UK in infancy can mitigate this effect. The data in table 2 further suggest that verbal IQ emerges at age 8 entirely unimpaired when treatment follows the current UK policy of keeping phenylalanine below 360 µmol/litre in early childhood.

The verbal to performance IQ discrepancy in favour of higher verbal skills concurs with previous findings.4-5 The significant difference in subscale scores is unlikely to have been an artefact of fluctuating test norms over time. WISC data summarised by Flynn consistently show rises in performance IQ compared with verbal IQ during the 1970s and 1980s,27 whereas in our study the direction of the subscale difference was the reverse, despite the median test date being 1986.

Key messages
- The lower than average IQ often found in treated phenylketonuria might be caused in part by specific weakness in spatial ability
- Conformity to current UK recommendations for phenylalanine concentrations at least in infancy is associated with normal verbal IQ in later childhood
- Better verbal than spatial intelligence in treated phenylketonuria might not be a function of dietary treatment factors or social status
there was no evidence from regression analyses that this test pattern could be attributed either to biochemical factors, at least in terms of lifetime phenylalanine exposure, or to social factors such as socioeconomic status. Furthermore, although a neurotoxic explanation is appealing on the grounds of performance IQ being a more sensitive index of brain damage than verbal IQ, and performance IQ measures being more representative of the fluid intelligence and executive functions that some authors believe are particularly vulnerable to raised phenylalanine concentrations, the results in table 2 contradict this view. If neurotoxic factors had been operating, a greater discrepancy would have been expected in the high rather than the low phenylalanine group, whereas the opposite was found to be the case.

The analyses of the subtest profile and verbal to performance IQ discrepancy were largely complementary, the uniformly depressed performance subtests indicating widespread difficulty with visuospatial reasoning, rather than a subtle pattern of discrete cognitive strength and weakness. Therefore, the evidence does not point to a distinctive signature of WISC subtest scores in treated phenylketonuria akin to that found—for example, in developmental dyslexia. However, the low information score conflicts with the view that spatial skills are exclusively weak and raises the possibility that factual knowledge also is underdeveloped.

Why then should verbal skill, with the exception of factual knowledge, be superior to spatial skill in treated phenylketonuria, especially in patients whose early phenylalanine control was optimal by nationally recommended standards? Our data support neither a neuropsychological explanation based on raised phenylalanine concentrations nor a sociological explanation based on social class. A third possibility is a developmental account based on idiosyncratic child rearing practices being hindered in early treated phenylketonuria, especially in children treated early for phenylketonuria. A fourth possibility is a developmental account based on dietary management of phenylketonuria.

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10 Diamond A. Phenylalanine levels of 6–10 mg/dl may not be as benign as once thought. Acta Paediatr 1994; 83(suppl 407):89–91.
The limping child

Among the complaints that ring alarm bells in paediatricians’ heads, back pain and a limp must come high on the list. The first prospective study of children presenting with a limp has been reported from Edinburgh (SU Fischer and TF Beattie. Journal of Bone and Joint Surgery [Br] 1999;81-B:1029–34).

In the first six months of 1996, 244 children aged 1–14 years presented to the accident and emergency department of the Royal Hospital for Sick Children with a limp and no history of trauma. One child was excluded from analysis because of inadequate records. These children represented 0.18% of attendances and 63% of them were boys. Their median age was 4.35 years. About one third presented on the day of onset of the limp and 85% within a week of onset. A diagnosis was not made in 72 children (30%). The most common final diagnoses were transient synovitis (23%), irritable hip (16%), and soft tissue injury or muscular strain (16%). Perthes’ disease, osteomyelitis, and slipped femoral capital epiphysis occurred in five, four, and one of the 243 patients. There is no mention of non-accidental injury.

Assessment included full clinical examination and usually full blood count and erythrocyte sedimentation rate (ESR). If the problem appeared to be in the hip, ultrasonography was performed by a consultant radiologist; x rays were obtained as clinically indicated. After making a working diagnosis, 20% of children were discharged without follow up, 57% were followed up in the accident and emergency department, 12% were referred for speciality follow up, and 12% were admitted to hospital. A diagnosis was missed on first assessment in three children: two developed osteomyelitis but neither of them had had the full blood count and ESR required by protocol, another child had Langerhans’ cell histiocytosis diagnosed radiologically after he had left the department.

With careful assessment in the emergency department most children presenting with a limp do not need to be admitted to hospital.
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