Phenylalanine blood levels and clinical outcomes in phenylketonuria: A systematic literature review and meta-analysis

Susan E. Waisbren a,*, Kay Noel b, Kyle Fahrbach b, Catherine Cella b, Diana Frame b, Alex Dorenbaum c, Harvey Levy a

a Children’s Hospital Boston, 1 Autumn Street, Room 525, Boston, MA 02115, USA
b United BioSource Corporation, 101 Station Landing, Medford, MA 02155, USA
c BioMarin Pharmaceutical Inc., 105 Digital Drive, Novato, CA 94949, USA

Received 11 April 2007; received in revised form 10 May 2007; accepted 10 May 2007
Available online 25 June 2007

Abstract

Blood phenylalanine (Phe) levels provide a practical and reliable method for the diagnosis and monitoring of metabolic status in patients with phenylketonuria (PKU). To assess the reliability of blood Phe levels as a predictive biomarker of clinical outcomes in the development of treatments for PKU, a systematic literature review and meta-analysis of published trials of PKU, which included Phe level and neurological and dietary compliance outcome measures, was conducted. Within-study correlations between Phe level and intelligence quotient (IQ) were extracted from 40 studies. Significant, proportional correlations were found during critical periods (from 0 to 12 years of age) for early-treated patients with PKU ($r = 0.35$; 95% confidence interval [CI]: $0.44$ to $0.27$), where each 100 μmol/l increase in Phe predicted a 1.3- to 3.1-point reduction in IQ. Similar significant correlations were observed between IQ and mean lifetime Phe level for early-treated patients ($r = 0.34$; 95% CI: $0.42$ to $0.25$), where each 100 μmol/l increase in Phe predicted a 1.9- to 4.1-point reduction in IQ. Moderate correlations were found between concurrent Phe level and IQ for early-treated patients. In conclusion, these results confirm a significant correlation between blood Phe level and IQ in patients with PKU, and support the use of Phe as a predictive biomarker for IQ in clinical trials.

**Keywords:** Biomarker; Predictive biomarker; Intelligence quotient

Introduction

Phenylketonuria (PKU) is an autosomal, recessive disorder involving mutations in the phenylalanine (Phe) hydroxylase gene, which inhibits the normal metabolism of Phe, an amino acid found in all proteins [1]. As a result, Phe cannot be converted to tyrosine and accumulates in the blood and other tissues [2].

Based on blood Phe levels, individuals affected with PKU are classified as having classic PKU (blood Phe: >1200 μmol/l), mild PKU (blood Phe: 600–1200 μmol/l) or non-PKU hyperphenylalaninemia (blood Phe: 120–599 μmol/l) [3]. More than half of patients affected have one of the milder clinical phenotypes [4]. The incidence of PKU varies considerably worldwide, with the highest rates seen in Ireland (approximately 1:4500) [5] and Eastern Europe (approximate rates for Estonia, Hungary and Latvia: 1:6000 [6], 1:9000 [7,8] and 1:8700 [9], respectively) and the lowest in Finland, Japan and Thailand (approximate rates: 1:100,000 [10], 1:108,000 [11] and 1:212,000 [12], respectively). With an incidence of approximately 1:10,000 in North America, it is estimated that more than 350 children in this continent are diagnosed with PKU each year and require lifelong treatment [13].

Untreated PKU is associated with severe mental retardation (IQ < 30), seizures, severe behavioral difficulties
and other symptoms [14–16]. Detection through neonatal screening programs and early initiation of treatment prevents the most severe neurological consequences of the disorder [17–19]. The only treatment currently available involves lifelong dietary measures [20], the continuation of which confers substantial health benefits to patients in adult life. Indeed, patients who maintain Phe-restrictive diets throughout childhood and into adolescence reported reduced rates of eczema, asthma, mental disorders, headache, hyperactivity and hypoactivity, compared with those who discontinue [21].

The PKU diet is highly restrictive, prohibiting the consumption of meat, fish, dairy products, nuts, beans and other protein-containing foods [22]. Measured amounts of fruits and vegetables are permitted in addition to special low-protein (low Phe) products [22]. A supplemental formula is required to provide the other essential amino acids, but has a strong taste and odor that many patients find unpalatable [23]. As a result, management of PKU is burdensome for both patients and their families, and adherence is a major medical problem [24–27].

Researchers in industry and academic centers began trials recently to assess potential therapies, including enzyme, amino acid or co-factor supplements, such as 6R-BH4 (sapropterin dihydrochloride). Study endpoints for these and other trials need to be determined. The present analysis was conducted to assess the use of blood Phe as a predictive biomarker for clinical outcomes in patients with PKU, based on an assessment of the global relationship between blood Phe and intelligence quotient (IQ).

Methods

A systematic review was performed using established best methods [28,29] to identify studies published between January 1980 and February 2004 that assessed Phe levels and neurological outcomes in patients with any clinical phenotype of PKU (classic/mild PKU or hyperphenylalaninemia). This process included developing a protocol in which objectives were stated, study sources and eligibility criteria were determined prospectively, key data elements were identified, and a preliminary analysis plan was outlined. Studies were reviewed for eligibility by at least two researchers. Extraction and consensus of data by two researchers served to confirm interpretation of published studies and as an error detection step.

Search strategy

Studies that assessed Phe levels and neurological outcomes and were published between January 1980 and February 2004 were identified by searching MEDLINE (via PubMed) using the terms diet OR dietary OR diet therapy [SH] OR phenylalaninemiblood OR “phenylalanine level” OR “phenylalanine levels” AND phenylketonuria [MeSH] OR phenylketonuria OR PKU OR hyperphenylalaninemia OR phenylketonuria with limits of English language, Human. In order to capture recent articles that may not have been indexed on MEDLINE, a keywords search was performed in PubMed for the past 6 months, with no publication type or language limits. Additionally, Current Contents® (Thomson Scientific, Philadelphia, PA, USA) was searched for the past year using analogous approaches. A manual search of reference lists in all accepted studies and recent reviews (last 2 years) was performed to supplement the electronic searches. In addition, a search for relevant systematic reviews and meta-analyses was carried out in the Cochrane Library in order to locate additional sources of citations. The literature search was supplemented by “best evidence”, largely comprised of out-of-print book chapters and consensus conference publications, to ensure that key results prior to 1980 were included in the review.

Eligibility criteria

Papers were selected for inclusion if they were human studies of any study design that included patients with any clinical phenotype of PKU (classic PKU, mild PKU or hyperphenylalaninemia) and reported assessments at baseline and study end point or cross-sectional for either (1) blood Phe and neurological (IQ, magnetic resonance imaging or neuro-physiological) outcome and/or (2) dietary Phe intake or blood Phe in relation to Phe threshold (compliance outcome). Accepted papers containing either within-study correlations of blood Phe and neurocognitive outcomes or sufficient individual patient data to permit calculation of within-study correlations were flagged for primary analysis.

Data extraction and analysis

For each accepted study, protocol-specific data were extracted by one investigator using a data extraction form (DEF) developed at the time of the project protocol. A second investigator checked the results by comparing all elements on the DEF with data in the original publication. Discrepancies in extracted data were resolved by a consensus conference between the two investigators and any disagreements were resolved by consulting with a third investigator. The consensus version of the extracted data was entered into a proprietary relational database of clinical trial data at UnitedBioSource Corp. Prior to locking the database for analysis, all data entries were 100% verified back to DEFS and the entire database was checked for accuracy via a 20% random sample check of data performed after completion of data entry. Error rates in excess of 2% would have triggered a 100% recheck of the entire database. The locked database was then exported for analysis.

In cases where there were multiple publications for the same patient population, the publication reporting the largest population was defined as the “parent” and other studies were reported as “kinds”; data from the entire group of studies were extracted and counted as a single study to avoid double counting in meta-analytic pooling.

As treatment scales varied widely across studies, meta-analyses were restricted to those studies reporting within-study correlations. Studies reporting multiple regression analyses to account for complex demographic, diagnostic and treatment variables were not included in the meta-analyses of studies reporting simple correlations, but were discussed separately. Data from studies reporting correlations between neuropsychological outcomes and blood Phe were found to be too disparate to be combined for meta-analyses.

Meta-analyses of within-study correlations between blood Phe levels and IQ were performed using random effects models [30] stratified, as data permitted, by type of disease (classic PKU, mild PKU, non-PKU hyperphenylalaninemia, mixed/unspecified) and blood Phe levels measured at different time points (critical period, lifetime, concurrent). The “critical period” reflected the time considered essential for structural development of the brain, and was defined variously by authors as the time from birth to 6–12 years of age. “Lifetime” Phe level was defined typically as the mean of 6- or 12-month median assessments for each patient, from birth to the last measurement in each study, and is described as a lifetime Index of Dietary Control (IDC). “Concurrent” assessments included Phe levels obtained at the time of testing of other clinical outcomes. Data from studies reporting correlations between cognitive outcomes other than IQ were too disparate to be combined for meta-analysis. Although studies used a variety of analytical methods for monitoring blood Phe levels, including chromatographic, enzymatic and fluorometric techniques, it was assumed that the analytical methods used in the specialized treatment centers performing the analyses yielded equivalent results. It was not possible to determine the time of the day when blood Phe monitoring samples were collected across the publications included in the meta-analysis.
To develop a quantitative proportional relationship between blood Phe and IQ, a meta-analysis of slopes was performed by determining the slope of Phe level predicting IQ, based on the meta-analytic correlation between Phe level and IQ, and the standard deviation (SD) for mean Phe and mean IQ. No formal statistical analyses were performed. Statistical significance was assumed where 95% confidence intervals (CI) did not cross zero.

Results

Searches yielded a total of 1153 citations. Of these, a total of 228 studies were accepted for inclusion in the database. Of these, 64 parent studies with 48 kin studies (publications describing preliminary results, subgroup results, other outcomes, or duplicate publications on the same patient population) reported within-study correlations of blood Phe and neurological outcomes (IQ, brain magnetic resonance imaging, or neuropsychological function measures) or provided sufficient individual patient data to permit calculation of such correlations (Table 1). The majority of studies used a retrospective, observational design (56%), took place in Europe (64%), and were published during the 1990s (59%). A total of 3361 patients were included and most had diagnoses of classic (34%) or unspecified PKU (46%).

Only 40 studies reported within-study correlations between blood Phe and IQ. Three studies that reported correlations between Phe level and IQ and Development Quotient [31–33] were excluded because such measurements in young children do not necessarily correlate with later assessments of IQ [34]. Meta-analyses were performed on subsets of subjects from these studies, defined by type of disease (classic, mild or mixed/unspecified) and type of blood Phe measured (critical, lifetime or concurrent). Key data from these 40 individual studies are available in Appendix I.

Meta-analyses of within-study correlations between Phe level and IQ were performed on subsets of patients, defined by type of disease and timing of Phe measurement.

Table 1
Characteristics of studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Studies (n = 64)</th>
<th>Patients (n = 3361)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980–1990</td>
<td>13</td>
<td>1579</td>
</tr>
<tr>
<td>1991–2000</td>
<td>38</td>
<td>1433</td>
</tr>
<tr>
<td>2001–2004</td>
<td>13</td>
<td>349</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>23</td>
<td>802</td>
</tr>
<tr>
<td>Europe</td>
<td>41</td>
<td>2559</td>
</tr>
<tr>
<td>Design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>14</td>
<td>605</td>
</tr>
<tr>
<td>Retrospective</td>
<td>36</td>
<td>2420</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>14</td>
<td>336</td>
</tr>
<tr>
<td>PKU population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>18</td>
<td>1548</td>
</tr>
<tr>
<td>Classic</td>
<td>33</td>
<td>1148</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>Hyperphenylalaninemia</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>Mixed/not recorded</td>
<td>10</td>
<td>587</td>
</tr>
</tbody>
</table>

PKU, phenylketonuria.

Meta-analyses of within-study correlations between IQ and Phe levels during the critical period are presented in Table 2. Results are presented for subgroups of children who were treated early and for mixed subgroups of early- and late-treated children. Statistically significant, moderate correlations [35] were observed between IQ and mean Phe levels during the critical period (0–12 years of age) for early-treated patients with PKU, as indicated by failure of the 95% CI to cross zero ($r = –0.35; 95\% CI: –0.44 to –0.27; n = 459$).

The imputed slopes between IQ and Phe level, based on meta-analytic correlations, and means and SD for Phe level and IQ, were similar for both early-treated patients with classic PKU ($r = –2.27; 95\% CI: –3.05 to –1.28$) and all early-treated patients ($r = –2.27; 95\% CI: –3.14 to –1.39$). Results indicate that a 100 μmol/l increase in Phe

Table 2
Meta-analyses of within-study correlations: intelligence quotient (IQ) and blood phenylalanine measured during the critical period

<table>
<thead>
<tr>
<th>PKU population</th>
<th>0–10 years of age</th>
<th>0–6 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$t$</td>
<td>$n$</td>
</tr>
<tr>
<td>Early treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>459</td>
</tr>
<tr>
<td>Classic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>382</td>
</tr>
<tr>
<td>Early treated</td>
<td>10</td>
<td>338</td>
</tr>
<tr>
<td>Mixed treatment history</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Mixed/unspecified</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>156</td>
</tr>
<tr>
<td>Early treated</td>
<td>3</td>
<td>147</td>
</tr>
<tr>
<td>Mixed treatment history</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

PKU, phenylketonuria; CI, confidence intervals. $t$, number of treatment groups contributing data; $n$, number of patients evaluated; $r$, correlation coefficient; **bold** indicates statistically significant correlations (95% CI does not cross zero).

*Two studies used in the analysis defined the critical period as 0–12 years.

*A negative correlation coefficient ($r$) indicates lower IQ with higher blood Phe levels.

* Significant between-study heterogeneity ($p < 0.10$).
during the critical period predicts an average 1.3- to 3.1-point reduction in IQ, over a range of Phe from 423–750 μmol/l (the range of Phe for the studies included in the meta-analysis).

Meta-analyses of within-study correlations between IQ and lifetime Phe levels are presented in Table 3. Statistically significant, moderate correlations between IQ and lifetime Phe level were observed for early-treated patients with PKU \( (r = -0.34; 95\%\ CI: -0.42 \text{ to } -0.25; n = 436) \).

The imputed slopes between IQ and lifetime Phe level were similar for both early-treated patients with classic PKU \( (r = -3.44; 95\%\ CI: -4.36 \text{ to } -1.94) \) and all early-treated patients \( (r = -2.92; 95\%\ CI: -3.89 \text{ to } -1.94) \). Results indicate that a 100 μmol/l increase in lifetime Phe predicts an average 1.9- to 4.1-point reduction in IQ, over a range of Phe from 394–666 μmol/l (the range of Phe reported in the studies included in the meta-analyses).

Meta-analyses of within-study correlations between IQ and concurrent Phe level are presented in Table 4. Statistically significant, moderate correlations were observed between IQ and concurrent Phe level for early-treated patients with PKU \( (r = -0.31; 95\%\ CI: -0.41 \text{ to } -0.20; n = 666) \).

The imputed slope between IQ and concurrent blood Phe was similar for both early-treated patients with classic PKU \( (r = -0.81; 95\%\ CI: -1.20 \text{ to } -0.41) \) and all early-treated patients \( (r = -1.41; 95\%\ CI: -1.55 \text{ to } -0.72) \), indicating that a 100 μmol/l increase in concurrent Phe predicts an average 0.5- to 1.4-point decrease in IQ, over a blood Phe range from 429–1644 μmol/l. Note that, unlike the correlations between IQ and critical period and lifetime Phe, which were based on longitudinal data, the correlations between IQ and concurrent Phe were largely derived from cross-sectional studies; accordingly, the results of correlations between IQ and concurrent Phe should not be applied to individual patients.

Dietary compliance data was reported for 928 patients in 24 studies (Appendix II). Thresholds for recommended Phe levels varied between studies from 300 to 900 μmol/l. Descriptive statistics for pooled data showed that 27% of children aged 0–6 years had Phe levels above recommended thresholds, and the percentage of patients whose blood Phe levels exceeded recommended thresholds increased with age. Indeed, in the two studies that reported adherence to treatment among patients aged older than 18 years, 78% of patients had Phe levels greater than recommended limits.

### Discussion

This systematic review and meta-analysis has documented a quantitative proportional relationship between Phe level and IQ. Each 100 μmol/l increase in Phe (assessed by mean IDC during the critical childhood period or lifetime through 18 years) predicted a 1.3- to 3.9-point decrease in IQ for early-treated patients with PKU, over a Phe range from 394 to 750 μmol/l. A correlation was also found between concurrent Phe level and IQ for early-treated patients with PKU, in which each 100 μmol/l increase in Phe predicted a 0.5- to 1.4-point reduction in IQ, over a Phe range from 429 to 1664 μmol/l.

Our findings were consistent, despite heterogeneity, in the patient populations that participated in the individual studies, including the type of PKU (classic, mild or non-PKU hyperphenylalaninemia), genotype, age, variable dietary restrictions, and adherence to treatment. Patients’ ages ranged from 0 to 39 years at study start, and not all patients received early treatment. Phe measurements were obtained only during childhood in some studies whereas
in other studies they were monitored throughout adulthood. In all, there were 12 different methods used to measure intelligence, including versions of the Wechsler Intelligence tests, the Stanford Binet Test of Intelligence, the Columbia Test of Mental Maturity, and the Culture Free Test. There were different versions with updated norms for the Wechsler Intelligence Scales, translations of the Wechsler tests and IQs derived from subtests of the Wechsler Intelligence Scale for Children. Combining results from different tests in meta-analytic studies is common [36]. However, there was initial concern about the validity of using so many different tests of intellectual functioning, particularly as studies assessed different aspects of intelligence. This concern dissipated as the findings from individual studies were found to be robust, confirming the relationship between Phe level and neurocognitive function.

Of note, the meta-analyses yielded similar correlations and slopes between IQ and Phe levels during both critical and lifetime periods. This may reflect the finding that lifetime and critical Phe levels (obtained no later than 12 years of age) were identical for several studies [32,37–40]. The remaining studies in the lifetime Phe meta-analysis included patients only up to 18 years of age [41–46]. The range of Phe levels during critical and lifetime periods, for which a fall in IQ was calculated, was relatively small (<400 μmol/l). In addition, definition of the critical periods was not uniform, and mean lifetime levels were dependent on the number of observations included in the calculations. Some individuals who discontinue treatment rarely undergo metabolic testing, while others monitor their Phe levels regularly. Thus, the mean lifetime levels and IDC as calculated here may not accurately represent lifetime blood Phe exposure. More information related to critical periods is needed to determine if declines associated with higher blood Phe levels during these periods continue throughout life or plateau after a certain age.

The findings from the meta-analyses are consistent with those of the British PKU Register (not included in our meta-analysis of simple correlations), in which multiple regression models incorporating IQ at age 4 years, social class, and parameters of diagnosis and treatment were documented [47,48]. Results showed that for each 300 μmol/l increase in Phe during the first 4 years of treatment, mean IQ fell by 0.67 SD (approximately 10 points) below the general population at 4 years of age.

Similarly, a previously published review of longitudinal studies of intelligence among early-treated patients with PKU concluded that for each 300 μmol/l increase in Phe level, IQ measured during pre-school years decreased by 0.5 SD (approximately 7 points) up to 10 years of age, after which time IQ remained reasonably stable [49]. Indeed, a longitudinal study by Huijbregts et al. showed that even small changes in Phe levels influenced the neuropsychological outcomes of patients with PKU, and indicated that young children were particularly sensitive to such fluctuations [50].

While there is broad consensus worldwide that dietary treatment to establish metabolic control of Phe levels should be initiated for infants with PKU who have Phe greater than 600 μmol/l [17], there is no consensus agreement on the optimal Phe levels during different age periods, either across different countries or among treatment centers in the USA. In US clinics, recommendations reported most commonly for patients with classic PKU are maintenance of Phe levels of 120–360 μmol/l (2–6 mg/dl) for those aged 12 years and under, and 120–600 μmol/l (2–10 mg/dl) for older patients [17].

The UK’s policy for dietary treatment recommends that Phe levels for infants and young children are maintained between 120 and 360 μmol/l (2–6 mg/dl), with relaxation of Phe control after childhood [51]. The German Working Group for Metabolic Diseases recommends maintenance of Phe levels of 40–240 μmol/l (0.7–4 mg/dl) until 10 years of age, 40–900 μmol/l (0.7–15 mg/dl) between 10 and 15 years, and 40–1200 μmol/l (0.7–20 mg/dl) beyond 15 years of age, combined with lifelong follow-up to detect possible late sequelae [32].

It is generally accepted that early-treated children with classic PKU suffer loss of IQ if the diet is discontinued, and children who continue the diet are more likely to achieve higher IQ scores and greater school achievement than those who discontinue [53]. A collaborative study conducted in the USA found a significant correlation between the age at which dietary control was lost (the age at the beginning of the first 6-month period in which the IDC exceeded 900 μmol/l) and the outcome observed. An earlier age of loss of dietary control corresponded to a lower IQ at 8 and 10 years of age compared with a child’s siblings or parents [18].

With the exception of one small (n = 31), controlled, prospective study that found no deterioration in cognitive ability in early-treated patients with PKU following diet relaxation at 5 years of age [54], published studies have reported significant reductions in the IQ of patients with PKU whose treatment is terminated in mid-childhood, and a lesser effect with relaxation of metabolic control [48,54–59].

Further support for strict dietary control (blood Phe ≤360 μmol/l) throughout the first decade of life is provided by studies assessing a broad range of cognitive functions. Several studies have reported a correlation between concurrent Phe level and performance on neuropsychological tests other than IQ, in children under 10 years of age [60–62].

Huijbregts et al. conducted a study comparing sustained attention in 57 early and continuously treated children with PKU aged 7–14 years, and 65 matched controls [61]. Compared with controls, patients with PKU and Phe levels greater than 360 μmol/l were less able to inhibit task-induced cognitive interference, exhibited lower speed of information processing, less consistent performance, and a greater reduction in performance level over time. Patients with concurrent Phe levels less than 360 μmol/l did not
differ from controls and were significantly better than patients with Phe levels greater than 360 μmol/l. Schmidt et al. reported that PKU patients aged 8.5–9 years with low concurrent Phe levels only performed better than patients with high Phe levels when long-term dietary control was good [63].

Despite the importance of adherence to dietary restrictions, there is widespread acknowledgment that adherence decreases with age. The three major collaborative studies demonstrated significant differences in IQ and cognitive test scores between groups of early-treated patients with classic PKU who maintain “good” and “intermediate” versus “poor” dietary compliance [52,54,64,65]. These studies also reported a steady rise in mean Phe levels beyond 4 years of age, occurring in parallel with relaxation of dietary restrictions. Consistent with these observations, most of studies in this meta-analysis that included patients aged older than 18 years, stated that patients were no longer on the restricted diet, and two studies found that 78% of patients had Phe levels above the recommended limits.

Although results of this meta-analysis do not define an optimal Phe level for early-treated patients with PKU, there is existing evidence from major collaborative studies to support the benefit of maintaining Phe levels lower than 600 μmol/l [52,64,65]. Future studies may show even stronger associations between Phe levels and other aspects of intellectual or cognitive functioning. For example, attention and executive functioning deficits are often reported in children with PKU who have a “normal” IQ [62,66,67]. Children with executive functioning deficits experience difficulties in attention, memory, organization, behavior regulation and academic achievement [68]. Thus, clinical studies that focus only on IQ may underestimate the true value of treatments that modestly lower Phe levels in patients with PKU.

In conclusion, this meta-analysis has demonstrated a quantitative, proportional relationship between blood Phe level and IQ for early-treated patients with PKU, assessed during critical, early childhood years (age 0–12 years) or by a lifetime IDC. A 100 μmol/l increase in Phe resulted in a 1.3- to 4.1-point reduction in IQ. A statistically significant, moderate correlation was also found between concurrent Phe level and IQ for early-treated individuals. These statistically significant correlations suggest that blood Phe level can be used reliably as a predictive biomarker for IQ in future clinical trials.

Acknowledgments

The authors thank MetaWorks Inc. for their assistance with the literature review and statistical analysis, and Dr. Hannah Wills for editorial support. Support for the meta-analysis was provided by BioMarin Pharmaceutical Inc.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ymgme.2007.05.006.

References


