Cognitive and Behavioral Development in Maternal Phenylketonuria Offspring

Susan E. Waisbren, PhD*, and Colleen Azen, MS‡

ABSTRACT. Objective. To assess cognitive and behavioral outcome in treated maternal phenylketonuria (PKU) offspring.

Methods. In this prospective, longitudinal study, 228 children who were born to mothers with treated PKU or untreated mild hyperphenylalaninemia were compared with 70 control subjects at 7 years of age.

Results. Offspring cognitive outcome negatively correlated with the number of gestational weeks that elapsed until maternal metabolic control was achieved (r = −0.61). Behavioral outcome was similarly affected. Postnatal measurement of stimulation in the home was also related to offspring IQ.

Conclusions. Children who are born to mothers who have PKU and attain metabolic control before or very early in pregnancy seem to begin life with undiminished potential. Delay in attainment of maternal metabolic control is associated with declines in offspring developmental outcome. The postnatal environment also significantly affects outcome. Interventions to improve dietary compliance before and throughout pregnancy as well as interventions to improve the postnatal home environment may reduce the risks associated with maternal PKU.

PEDIATRICS 2003;112:1544–1547; maternal phenylketonuria, maternal PKU, cognitive outcome, behavioral outcome.

ABBREVIATIONS. Phe, phenylalanine; PKU, phenylketonuria; MHP, mild hyperphenylalaninemia; HPA, hyperphenylalaninemia.

The present study includes school-age assessments of cognitive development, motor skills, expressive and receptive language, attention, daily living skills, achievement, emotional well-being, and behavior. Environmental influences such as prenatal exposure to elevated phenylalanine (Phe) levels, maternal IQ, maternal age, socioeconomic position, and stimulation in the home were considered.

METHODS

Sample

As noted in Table 1, 501 offspring of mothers who were enrolled in the Maternal PKU Collaborative Study were eligible for cognitive and behavioral evaluations. Eight offspring died before receiving a cognitive and behavioral evaluation, and the mothers of 44 (9%) offspring declined additional participation or were lost to follow-up. Two offspring with phenylketonuria (PKU) were excluded, but 2 who had mild hyperphenylalaninemia (MHP) that did not require treatment were included.

Among the 401 maternal PKU offspring eligible to participate, 366 received at least 1 cognitive and behavioral assessment, representing an overall accrual rate of 91%, and 228 (57%) received an evaluation at the age of 7 years. Equal numbers of boys and girls were tested. Children who received evaluations had significantly lower average Phe exposure in utero (P = .019) than children who did not receive assessments. However, the groups did not differ in terms of child sex, maternal IQ, maternal age, maternal education, socioeconomic position, or timing of maternal metabolic control.

Procedures

A network of psychologists performed the majority of evaluations, usually in the homes of the participants. Data collection procedures have been described previously.

Analyses

The hyperphenylalaninemia (HPA) sample was divided according to timing of maternal metabolic control, defined as the number of gestational weeks after which blood Phe levels remained consistently <600 µmol/L throughout the remainder of the pregnancy. When sample size permitted, analyses were also performed with the more stringent definition of maternal metabolic control as maintenance of blood Phe levels between 120 and 360 µmol/L.

Analyses were performed using STATA 6.0. Pearson correlation analysis was used to evaluate the relationship of maternal demographic and treatment factors to offspring outcome, when normal distributions were confirmed. Analysis of variance was used to compare continuous outcome variables among the various maternal Phe-control subgroups, with Dunnett’s method for pairwise comparisons of each subgroup to control subjects. Multiple logistic regression analyses were performed to investigate predictors of categorical outcomes. Nonparametric methods such as rank sum tests, Wilcoxon tests, and Fisher exact tests were used, as needed, for categorical outcomes or when continuous variables deviated from normality. When multiple comparisons were made among subgroups, Bonferroni adjustment was applied to P values.

RESULTS

By 7 years of age, 18% of children who were born to mothers with PKU performed in the range of mental retardation, 18% attained scores in the borderline range, and 64% could be considered average or above in terms of their intellectual abilities. As noted in Table 2, scores on the Wechsler Intelligence Scale for Children–Revised declined with weeks that elapsed until maternal metabolic control was achieved (r = −0.61, P < .0001). On every subscale as well, the timing of maternal metabolic control was negatively correlated with offspring performance. This held true for tests of memory, language, behavior, achievement, and visual motor skills. When the more stringent criteria for maternal metabolic control was applied (blood Phe levels 120–360 µmol/L), the correlation with full-scale IQ remained significant.
TABLE 1. Total Sample and Number Receiving Cognitive and Behavioral Assessments

<table>
<thead>
<tr>
<th></th>
<th>Offspring From HPA Pregnancies</th>
<th>Control Subjects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled in MPKUCS</td>
<td>401</td>
<td>100</td>
<td>501</td>
</tr>
<tr>
<td>Receiving assessments</td>
<td>366</td>
<td>91</td>
<td>457</td>
</tr>
<tr>
<td>%</td>
<td>91</td>
<td>91</td>
<td>91</td>
</tr>
</tbody>
</table>

MPKUCS indicates Maternal PKU Collaborative Study.

Results of School-Age Assessments: Wechsler Intelligence Scale for Children

TABLE 2. Results of School-Age Assessments: Wechsler Intelligence Scale for Children–Revised

<table>
<thead>
<tr>
<th>Weeks to Metabolic Control (Levels &lt;600 μmol/L)</th>
<th>Non-HPA Control</th>
<th>Untreated MHP</th>
<th>Before Pregnancy</th>
<th>&gt;0–10</th>
<th>&gt;10–20</th>
<th>&gt;20 or Never in Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>63</td>
<td>36</td>
<td>39</td>
<td>46</td>
<td>44</td>
<td>70</td>
</tr>
<tr>
<td>Mean age (mo)</td>
<td>89 ± 7</td>
<td>86 ± 7</td>
<td>84 ± 9</td>
<td>86 ± 9</td>
<td>87 ± 9</td>
<td>86 ± 9</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>109 (39–147)</td>
<td>106 (63–125)</td>
<td>105 (73–126)</td>
<td>100 (74–139)</td>
<td>93 (35–123)</td>
<td>72 (35–133)</td>
</tr>
<tr>
<td>% with IQ ≥85</td>
<td>2</td>
<td>17</td>
<td>5</td>
<td>24</td>
<td>27*</td>
<td>66*</td>
</tr>
<tr>
<td>% with IQ &lt;70</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>Verbal score</td>
<td>108 (46–154)</td>
<td>105 (67–125)</td>
<td>103 (75–129)</td>
<td>96 (65–142)</td>
<td>93 (40–122)</td>
<td>77 (40–127)</td>
</tr>
<tr>
<td>Performance score</td>
<td>111 (44–142)</td>
<td>104 (71–129)</td>
<td>102 (72–129)</td>
<td>95 (69–128)</td>
<td>96 (40–129)</td>
<td>72 (40–131)</td>
</tr>
</tbody>
</table>

Data are median scores and range.
* Bonferroni-adjusted P < .025 for comparison with control subjects.
† Bonferroni-adjusted P < .0001 for comparison with control subjects.

DISCUSSION

The results of this study suggest that cognitive and behavioral problems associated with maternal PKU are real and long lasting. At each time period, the correlation between the timing of maternal metabolic control and offspring outcome was significant. When the more stringent definition of maternal metabolic control requiring blood Phe levels between 120 and 360 μmol/L as opposed to levels between 120 and 600 μmol/L was applied, the percentage of children who performed in the borderline range or range of mental retardation among women who attained metabolic control before 20 weeks’ gestation declined. Similarly, the percentage of children who exhibited behavior problems declined. These data indicate that the more stringent criterion for metabolic control is warranted.

Offspring of women with untreated MHP performed similarly to control subjects. At 7 years of age, only 1 child who was born to a mother with untreated MHP evidenced signs of mental retardation, and 14% had severe behavior problems. In the control group, 1 child performed in the range of mental retardation and 23% had severe behavior problems.

Offspring of optimally treated women who had...
Environmental Influences at 7-Year Assessment

Data are median scores, ranges and sample sizes.

TABLE 5. Background and Environmental Factors—Logistic Regression Analysis: Risk for Attaining Metabolic Control After 10 Weeks’ Gestation in Relation to Maternal Factors (Excludes Untreated MHP)

<table>
<thead>
<tr>
<th>Conditional Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (&lt; 21 y)</td>
<td>4.72 (1.65–13.55)</td>
</tr>
<tr>
<td>Maternal IQ (IQ &lt; 85)</td>
<td>2.04 (1.06–3.93)</td>
</tr>
<tr>
<td>SES (lowest quartile)</td>
<td>1.31 (0.63–2.70)</td>
</tr>
<tr>
<td>Marital status (single)</td>
<td>3.49 (1.55–7.87)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; SES, socioeconomic status.

PKU and attained metabolic control before conception did not differ from control children. This held true when maternal blood Phe levels remained between 120 and 600 μmol/L as well as when levels were between 120 and 360 μmol/L. These optimally treated children scored higher on cognitive and behavioral tests than offspring of treated women who attained metabolic control after pregnancy began but before 10 weeks’ gestation, although this difference was not statistically significant.

Approximately 16% of treated women with HPA attained metabolic control between 10 and 20 weeks’ gestation. The developmental outlook for their offspring varied, with 73% of children performing within the average intellectual range at 7 years of age but 27% performing in the borderline range and 7% performing in the range of mental retardation. Language deficits and academic difficulties were also more frequent.

Assessments obtained when the children were 7 years of age indicated that weaknesses in language were present as well as weaknesses in other developmental domains. A recent study comparing maternal PKU offspring with children with PKU and control subjects confirmed these findings and suggested an increased risk among maternal PKU offspring for executive function deficits and attention-deficit/hyperactivity disorder.11

Despite a highly significant correlation between maternal metabolic control and offspring outcome, exceptions to the rule frequently occurred. Some children who were born to poorly treated mothers developed normally, and some children who were born to very well-treated mothers experienced mental retardation. Heterogeneity might be attributable to differences in timing and level of exposure. The impact of a relatively low level of exposure over a long period of time may not be comparable to the impact of high levels over a short period of time.12 Heterogeneity might also reflect genetic differences in mothers.13

These findings point to the primacy of maternal metabolic control during pregnancy in predicting offspring outcome, yet postnatal factors cannot be ignored. All but a few of the women who were enrolled in the study had terminated the diet during middle childhood and resumed treatment only for purposes of pregnancy. The vast majority discontinued treatment as soon as the infant was born. Elevated Phe levels, associated with reductions in
cognitive abilities, depression, anxiety, and other emotional difficulties,\textsuperscript{14} may have compromised their parenting abilities. In the present study, the median maternal IQ among women with HPA was 85 (range: 40–130) compared with 101 (range: 79–126) for control subjects ($z = 6.57, P < .0001$). Significantly more women with PKU experienced lower socioeconomic conditions. These factors, associated with less stimulation in the home, increased the risk for a low IQ in the offspring.

In the general population, heritability of IQ is in the 0.40 to 0.50 range,\textsuperscript{15} and the correlation between child IQ and socioeconomic status is approximately 0.30.\textsuperscript{16} In this study, the correlation of HPA offspring IQ with maternal IQ was 0.41 and with socioeconomic status was 0.48. In the literature, additional variance in child IQ can be explained when other risk factors are added to the equation (including biological influences, multiple moves, single-parent families, deaths, loss of employment, and other stresses).\textsuperscript{17,18} This suggests that cumulative risk contributes more significantly to eventual outcome than single-risk factors. This is particularly true in maternal PKU, for which risk factors include the biological risk of elevated exposure to Phe in utero plus low maternal IQ, low socioeconomic status, and a lack of stimulation in the home. Offspring outcome, therefore, may differ because of idiosyncratic combinations of genetic and environmental factors in each child.\textsuperscript{19} The analogy of signal-to-noise applies: “The ‘signal’ of early medical and biological influences on outcome is gradually obscured by the ‘noise’ generated by the environment.”\textsuperscript{15}

Only longer-term follow-up can determine whether maternal PKU offspring will grow up to “love and work.” For children whose mothers attained metabolic control after 20 weeks’ gestation, the outlook seems bleak, and for those whose mothers attained metabolic control between 10 and 20 weeks’ gestation, the outlook is mixed. Many of these children experience difficulties communicating, delays in development, poor academic achievement, and serious behavior problems that potentially limit social relationships and ability to secure employment. Children who are born to mothers who attain metabolic control before or very early in pregnancy seem to begin life with undiminished potential. However, they face environmental risks associated with their mother’s PKU. Interventions and research focused on these factors may be most productive in reducing adverse outcomes in maternal PKU.

\section*{ACKNOWLEDGMENTS}

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\section*{REFERENCES}

2. Stata Statistical Software: Release 6.0 (computer program). College Station, TX: Stata Corporation; 1999
5. Hammill DD, Newcomer PL. Test of Language Development—Primary. 2nd Ed. Austin, TX: Pro-Ed; 1988
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