Executive Functioning of 4 Children With Hyperphenylalaninemia From Childhood to Adolescence

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Dr Sharman conceptualized and designed the study, collected the phase 2 data, carried out the analyses, and drafted the initial manuscript; Dr Jones collected the phase 1 data, carried out the initial analyses, and reviewed and revised the manuscript; Drs Sullivan, Young, and McGill supervised the study, provided specific expert advice as per their clinical qualifications in the design of the study, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Hyperphenylalaninemia is a variant of phenylketonuria, and debate remains as to what, if any, active management of this condition is required to preserve cognitive function and psychological well-being. This study is the first to examine longitudinally the executive function (EF) in adolescents with hyperphenylalaninemia. Two sibling pairs with mild hyperphenylalaninemia underwent neuropsychological examination in early childhood and again in adolescence using EF tests that were highly sensitive to phenylalanine exposure. By early adolescence, none of the 4 children demonstrated EF impairment. The children demonstrated a typical developmental trajectory of EF from childhood to adolescence, given phenylalanine exposure consistent with their condition.

Hyperphenylalaninemia is a variant (milder version) of phenylketonuria (PKU). Although strict dietary control of phenylalanine and regular phenylalanine monitoring of children with PKU remains an unequivocal treatment plan to prevent neurologic damage, recent debate has reignited the question of whether children with hyperphenylalaninemia require active treatment, and if so, at what level of phenylalanine exposure treatment should commence. Previous research into the neuropsychological outcomes of children with hyperphenylalaninemia found that function ranges from normal to showing mild EF deficit. There are few published studies regarding the outcome of children with hyperphenylalaninemia, and anecdotal reports suggest that treatment is highly variable (ranging from monitoring only, to some restrictions of protein in diet and supplemental formula). A recently released guideline from the American College of Medical Genetics suggests no need for treatment with "natural" phenylalanine levels between 120 and 360 µmol. There exists international variation between classifications of PKU subtypes (eg, hyperphenylalaninemia, mild hyperphenylalaninemia, non-PKU hyperphenylalaninemia, mild PKU, etc) and their associated neuropsychological deficits (or not, as the case may be). The research into outcomes of children with hyperphenylalaninemia has been further confounded by a focus on assessments of global scores of intellectual function (eg, IQ scores) rather than an assessment of the more subtle executive function (EF) deficits known to typify the neuropsychological profile of those with PKU.

This study was part of a larger longitudinal analysis in a cohort of children with PKU originally tested in 2001/2002 and retested in 2009 on EF measures. In the original data set, 4 children (2 sibling pairs) with hyperphenylalaninemia were included. Given the paucity of research to inform treatment guidelines for these children, this study presents their EF results with the use of a selection of EF tests.
that have previously demonstrated strong associations with phenylalanine variations. Executive functioning tests were administered in 2009; alongside those tests suitable for retesting from the 2001/2002 data set. To the authors’ knowledge, this is the first longitudinal study examining the cognitive development in children with hyperphenylalaninemia. These data may assist in moving toward a better understanding of the potential treatment requirements of this population. Because only 4 children were available, the data are presented in a largely descriptive format.

**CASE REPORT**

Ethical approval for the study described was obtained from the Queensland University of Technology Human Research Ethics Committee and the Royal Children’s Hospital, Brisbane, Queensland, Ethics Committee. Written parental consent was obtained at both testing periods, as well as written child consent at the second testing period (adolescence). Two sibling pairs (3 boys, 1 girl) with hyperphenylalaninemia were assessed in 2001/2002 at a mean age of 4.66 years and again in 2009 at a mean age of 12.45 years on the EF measures reported below. The metabolic dietitian advised that all 4 children were adhering to a protein-restricted diet (but much less restricted than the classic PKU diet) and that they were cautiously treated and therefore prescribed enough PKU supplemental formula to ensure a minimum intake of 1 g protein/kg of body weight per day.

In 2001/2002, testing took place in the children’s home and was conducted by Dr Toni Jones. In 2009, testing took place on-site at the Royal Children’s Hospital Queensland and was conducted by Dr Rachael Sharman. Dr Sharman was blind to the adolescents’ biochemical levels and previous EF results at the time of testing. The children completed the following tests at a mean age of 4.66 years (age range: 3 years, 5 months, to 6 years, 11 months) and ~8 years later at a mean age of 12.45 years:

1. Rey-Osterreith Complex Figure Test:<sup>9</sup> a commonly used test of visuospatial planning (standard scoring)
2. Wechsler Intelligence Scale for Children, Fourth Edition<sup>10</sup>, Digit Span: a working memory subtest
3. Neuropsychological Assessment II<sup>11</sup> Comprehension of Instructions: a comprehension task that involves a component of working memory (a series of instructions that need to be performed in a specific order and become increasingly lengthy and complex)

At the 2009 testing, the adolescents also completed the NEPSY-II Inhibition Task<sup>11</sup>: this is a Stroop-type test highly similar to Diamond et al.'s<sup>12</sup> original (day-night) Stroop task, which suggested that children with well-controlled PKU may still show subtle deficits. Children progress through 3 stages of the task, culminating in them holding and switching between 2 rules in mind, while inhibiting a prepotent response. Parents also completed the Behavior Rating Inventory of Executive Function<sup>13</sup>, an ecologically valid measure of EF recommended by the Waisbren and White<sup>14</sup> review of the most appropriate instruments for assessment of EF in children with PKU.

Phenylalanine and tyrosine levels of these 4 children were available from infancy to the day of testing. Newborn screening phenylalanine values ranged from 320 to 550 μmol. Minimum monthly testing of phenylalanine was recorded across their lifetimes. Tyrosine levels were available on a sporadic basis before the year 2000 and at all phenylalanine testing points after the year 2000. Lifetime mean (SD) phenylalanine was 227 (20.7) μmol, lifetime mean tyrosine was 85 (17) μmol, lifetime mean phenylalanine: tyrosine ratio was 3.2 (0.79), concurrent mean phenylalanine was 295 (48) μmol, concurrent mean tyrosine was 80 (23.4) μmol, and concurrent mean phenylalanine: tyrosine ratio was 4 (1.9).

Phenylalanine tolerance testing had also taken place for the participants at age 5 years and in early adolescence. Tolerance at age 5 years ranged from 40 to 66 mg/kg per day and in early adolescence from 55 to 63 mg/kg per day (note there were data for 3 of 4 participants only at adolescence). According to Campistol et al.,<sup>2</sup> the combination of their mean phenylalanine levels and tolerance places these children in the mild hyperphenylalaninemia range.

Further analysis of the children’s phenylalanine levels showed they rarely exceeded 400 μmol at any 1 point during their lifetime. Their historical records indicated that 3

### TABLE 1 Neuropsychological Performance of 4 Adolescent Children with Mild Hyperphenylalaninemia

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<thead>
<tr>
<th></th>
<th>Childhood</th>
<th>Adolescence</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>RCFT</td>
<td>N/A</td>
<td>Both normal&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>WISC-DS CI</td>
<td>9.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 and 12&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>NEPSY-II CI</td>
<td>12.75 (1.7)</td>
<td>11–15</td>
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<tr>
<td>NEPSY-II Inh</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>NEPSY-II Inh Error</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>BRIEF GEC</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>BRIEF WM</td>
<td>N/A</td>
<td>N/A</td>
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</tbody>
</table>

*BRIEF, Behavior Rating Inventory of Executive Function; CI, Comprehension of Instructions; GEC, Global Executive Composite; Inh, Inhibition; NEPSY-II, ; RCFT, Rey-Osterreith Complex Figure Test; WISC-DS, Wechsler Intelligence Scale for Children, Fourth Edition, Digit Span; WM, Working Memory.

<sup>a</sup>Based on 2 participants only who were old enough at the time for scoring purposes; scores for the childhood digit span were calculated by using the earlier version of the Wechsler Intelligence Scale for Children (Third Edition).
of the children demonstrated a phenylalanine level >400 μmol (1 child had a maximum of 420 μmol on 1 testing occasion, 1 child had a level of 470 μmol on 1 testing occasion, and 1 child had levels of 420 and 430 μmol on 2 testing occasions, respectively).

Table 1 presents means, SDs, and ranges for the EF tests. Rey-Osterreith Complex Figure Test performance was scored as either normal or impaired according to age-expected norms at both time points (early childhood and again at adolescence). The Wechsler Intelligence Scale for Children, Fourth Edition, Digit Span, and NEPSY II language comprehension task and inhibition (Stroop) tasks are represented as scaled scores (10 = average, 3 = 1 SD; higher scores represent better function). The Behavior Rating Inventory of Executive Function results are represented by t-scores (average = 50, 10 = 1 SD; higher t-scores represent higher levels of impairment). Clinically, EF impairment is suggested if any individual score is ≥1.5 SDs worse than the age-expected mean.

Table 1 shows that these 4 children with mild hyperphenylalaninemia performed within normal ranges on every task (ie, no individual child performed ≥1.5 SDs worse than the age-expected norm). No deterioration in performance was apparent from childhood to adolescence on the 3 tests available for longitudinal analysis.

**DISCUSSION**

This longitudinal investigation was conducted across the developmental period thought to be highly sensitive to phenylalanine exposure by using measures of EF known to be highly sensitive to variations in phenylalanine. By early adolescence, these 4 children with mild hyperphenylalaninemia did not demonstrate EF impairment and appeared to have maintained their normal developmental trajectory of EF from childhood to adolescence.

This case study needs to be replicated in larger samples to ensure generalizability. In addition, because testing of cognitive function first occurred at a mean age of 4.66 years, it is possible that early exposure to phenylalanine could have affected EF before the first testing point, and it is impossible to ascertain the true potential for EF and cognitive ability these children may have been born with.

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