NEUROCOGNITIVE, OUTCOMES IN PKU: IT’S TIME TO RAISE THE BAR

KEY POINTS
1. High Phenylalanine (Phe) levels harm the brain.
2. Traditional therapies do not completely protect individuals with PKU.
3. New approaches may improve outcomes in PKU.

KEY POINT #1: PHE IS HARMFUL


BLOOD PHE AND IQ ARE CORRELATED IN PATIENTS WITH PKU

<table>
<thead>
<tr>
<th>Observation period</th>
<th>Range of blood Phe (μmol/L)</th>
<th>Lifetime IQ loss for each 100 μmol/L increase in blood Phe (IQ points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical period (0–12 years old)</td>
<td>423–750</td>
<td>1.3–3.1</td>
</tr>
<tr>
<td>Lifetime (all ages)</td>
<td>394–666</td>
<td>1.9–4.1</td>
</tr>
</tbody>
</table>

OUTCOMES FOR ADULTS WITH PKU WORSE FOR THOSE WHO DISCONTINUED DIET

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Discontinued Diet</th>
<th>Continued Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Problems (per PKU patient)</td>
<td>2.4 ± 1.8</td>
<td>0.9 ± 1.4</td>
</tr>
<tr>
<td>College Degree</td>
<td>32%</td>
<td>78%</td>
</tr>
<tr>
<td>Socioeconomic Class I or II*</td>
<td>19%</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Two highest socioeconomic classes in the Hollingshed classification system


STABILITY OF BLOOD PHE

- Correlation of SD of blood Phe levels with FSIQ was -0.36 (p = 0.058)
- FSIQ decreased 4.3 points with 1 point increase in SD of blood Phe

Example Low Variability IQ = 116
Example High Variability IQ = 92

Mean* (412 μmol/L) ± SD† (166 μmol/L)
Mean* (389 μmol/L) ± SD† (325 μmol/L)

*Lifetime blood Phe levels
†Mean standard deviations for lifetime blood Phe levels

Example Low Variability IQ = 116
Example High Variability IQ = 92

Mean* (412 μmol/L) ± SD† (166 μmol/L)
Mean* (389 μmol/L) ± SD† (325 μmol/L)

*Lifetime blood Phe levels
†Mean standard deviations for lifetime blood Phe levels

DOPAMINE: EXECUTIVE FUNCTION, EMOTION AND SOCIAL BEHAVIOR

- Neurotransmitter related to attention, mood, and movement
- Precursor to norepinephrine, epinephrine, and other neurotransmitters

DOPAMINE IS SYNTHESIZED FROM TYROSINE THAT IS CONVERTED TO L-DOPA

Periphery (mostly liver) Blood Brain Barrier Brain
Phenylalanine PAH Tyrosine TH L-dopa AADC Dopamine
BH4 = tetrahydrobiopterin
PAH = phenylalanine hydroxylase
TH = tyrosine hydroxylase
AADC = aromatic amino acid decarboxylase

DOPAMINE ACTIVITY IS REDUCED IN ADULTS WITH PKU

FDOPA uptake in first 6 minutes after injection is reduced in PKU

Rate of FDOPA utilization is reduced in striatum of PKU patients

MYELIN INSULATES AXONS WHICH INCREASES THE SPEED OF PROCESSING OF NERVE SIGNALS

White matter contains nerve fibers surrounded by myelin

CONTRIBUTIONS OF PREFRONTAL CORTEX TO MENTAL FUNCTION

- Executive Functions
  - Cognitive abilities that control and regulate other abilities and behaviors
  - Include
    - Planning
    - Attention
    - Working memory
    - Problem solving
    - Impulse control
- Social Behaviors
- Emotional Responses
WHITE MATTER HYPOTHESIS

- Individuals with PKU have abnormal white matter
- Abnormalities may be due to
  - Increased myelin turnover
  - Elevated water content
  - Disturbed myelin synthesis
- White matter abnormalities may reduce speed of processing leading to neurocognitive deficits observed with PKU


KEY POINT #2: TRADITIONAL THERAPIES NOT COMPLETELY PROTECTIVE

- Nearly one in three PKU children under the age of 10 have blood Phe above recommended target range
- Noncompliance increases as patients enter adolescence

Adapted from Table 2 of Walter JH, et al. Lancet. 2002;360:55–57.

ADHERENCE TO TREATMENT

- Nearly one in three PKU children under the age of 10 have blood Phe above recommended target range
- Noncompliance increases as patients enter adolescence

Adapted from Table 2 of Walter JH, et al. Lancet. 2002;360:55–57.

NEUROCOGNITIVE DEFICITS IN TREATED PKU

REDUCTIONS IN:
- Executive Functioning
- Memory
- Planning
- Attention
- Organization
- Mental Processing Speed
- Behavior and Mood
- Success in school and life

Blood Phe not consistently in target range


EXECUTIVE FUNCTION DEFICITS

Even with early and continuously treated PKU, executive function gets worse with age and rising Phe levels

EXECUTIVE FUNCTIONING DEFICITS

% Children in Severe Range

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 80)</th>
<th>Hydrocephalus (n = 45)</th>
<th>PKU (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>18*</td>
<td>21*</td>
</tr>
</tbody>
</table>

*P < 0.001 compared to control

**Based on Behavior Rating Inventory of Executive Function (BRIEF) global executive composite score. Severe range is > 1 SD above the mean.


ATTENTION PROBLEMS

Simulant Treatment for Attentional Dysfunction

<table>
<thead>
<tr>
<th>Group</th>
<th>PKU (n = 38)</th>
<th>Diabetes Mellitus (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26%*</td>
<td>7%</td>
</tr>
</tbody>
</table>

*P < 0.001 compared to control with diabetes mellitus


WORKING MEMORY

Mean Span

- Verbal
- Object
- Spatial

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 20)</th>
<th>PKU (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.2</td>
<td>4.6*</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>3.4*</td>
</tr>
<tr>
<td></td>
<td>3.8</td>
<td>3.3*</td>
</tr>
</tbody>
</table>

*P < .05 compared to control


STRATEGIC PLANNING

Normative Data PKU

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normative Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Scanning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letter Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switching</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| *P < .05 compared to control data


ORGANIZATION AND MEMORY

Words Recalled

- California Verbal Learning Test

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 23)</th>
<th>PKU (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger &lt; 11 yo</td>
<td>8.3</td>
<td>5.5</td>
</tr>
<tr>
<td>Older ≥ 11 yo</td>
<td>8.3</td>
<td>7.6</td>
</tr>
</tbody>
</table>

*P = 0.05 compared to control


IMPULSE CONTROL

Number of Errors

- Go
- No-Go

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n = 23)</th>
<th>PKU (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go</td>
<td>25</td>
<td>32</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to control

Christ et al., 2006


Christ et al., 2000
RESPONSE MONITORING

- *Control* vs. *PKU* for Simple RT, Go RT, and Post-Error RT
- Reaction Time (msec)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Simple RT</th>
<th>Go RT</th>
<th>Post-Error RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>375</td>
<td>448</td>
<td>601</td>
</tr>
<tr>
<td>PKU</td>
<td>335</td>
<td>617</td>
<td></td>
</tr>
</tbody>
</table>

*P < .05*

Araujo et al., in press (request reprint from D. White)

EXECUTIVE FUNCTIONING IN PKU

- Planning diet
- Remembering Phe intake for records
- Remembering to take formula
- Helps with inhibiting responses, resisting foods not allowed on diet
- Maintaining supplies
- Monitoring blood Phe and making appropriate adjustments in intake

MENTAL PROCESSING SPEED

- Symbol Search Coding
- Contingency Naming

<table>
<thead>
<tr>
<th>Test</th>
<th>Control</th>
<th>PKU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symbol Search</td>
<td>12 ± 2 (mean + SE)</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Coding</td>
<td>10 ± 2</td>
<td>12 ± 2</td>
</tr>
<tr>
<td>Naming</td>
<td>18 ± 2</td>
<td>20 ± 2</td>
</tr>
<tr>
<td>Contingency</td>
<td>8 ± 2</td>
<td>10 ± 2</td>
</tr>
</tbody>
</table>

*P < 0.01 for control group compared to PKU group


META-ANALYSIS SUMMARY

- Meta-analysis of 11 studies demonstrates deficits in multiple cognitive domains

- IQ Processing Speed
- Attention
- Inhibition
- Motor Control
- Working Memory

- Hedge’s g effect size with 95% confidence intervals

Adapted from Figure 1 of Moyle JJ, et al. Neuropsychol Rev. 2007;17(2):91-101.

SCHOOL PROBLEMS

- PKU Students (n = 26)
- Unaffected Peers (n = 21)
- Total school problems
- Required special tutoring
- Repeated classes

<table>
<thead>
<tr>
<th>Problem</th>
<th>PKU Students</th>
<th>Unaffected Peers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total school problems</td>
<td>50%*</td>
<td>12%</td>
</tr>
<tr>
<td>Required special tutoring</td>
<td>39%</td>
<td>24%</td>
</tr>
<tr>
<td>Repeated classes</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Shy/withdrawal</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*P = 0.028 vs controls


EMOTIONAL AND BEHAVIORAL OUTCOMES

- DEPRESSION
- ANXIETY
PSYCHIATRIC OUTCOMES IN ADULTS WITH PKU

* P < 0.05 as compared to 18-year-old controls


AGORAPHOBIA

Blood Phe level and score on AAL Scale† are significantly correlated

†From the Mobility Inventory, measuring avoidance behavior when alone (AAL)

Blood Phenylalanine Level (μmol/L)

rs = 0.43

KEY POINT #3: IMPROVEMENTS IN OUTCOME MAY BE POSSIBLE

GREATER UNDERSTANDING OF PSYCHOLOGICAL FACTORS

Social Support

Positive Attitudes

Manageability


GREATER VARIETY OF FORMULAS AND FOODS

NEW THERAPIES

- Large Neutral Amino Acids (LNNA’s)
  Available
- Tetrahydrobiopterin Therapy (BH4)
- Ammonia Lyase
  - Enzyme Replacement Therapy In research
- Gene Therapy
ASSESSMENT OF OUTCOMES

Identify deficits associated with PKU

Track changes over time (impact of changes in blood level or therapeutic strategies)

Uniform set of tests

Can be administered by non-psychologists

UNIFORM ASSESSMENT METHOD

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>INFANTS (0-2 YRS)</th>
<th>CHILDREN (3-17 YRS)</th>
<th>ADULTS (18+ YRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Behavior</td>
<td>ABAS-II</td>
<td>ABAS-II</td>
<td>ABAS-II</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>--</td>
<td>BRIEF</td>
<td>BRIEF</td>
</tr>
<tr>
<td>Social/Emotional Functioning</td>
<td>--</td>
<td>BASC-II</td>
<td>BDI-II &amp; BDI-II</td>
</tr>
</tbody>
</table>

ABBREVIATIONS & SOURCES

• BRIEF: Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, Kenworthy, 2000)
• BAI: Beck Anxiety Inventory (Beck, Steer, 1993)

FOR MORE INFORMATION AND SCORING

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THANK YOU!