Neurocognitive and Behavioral Issues in PKU

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Desiree White, PhD, has received research grants/support from, served as a consultant for, and received honoraria from BioMarin.
Educational Learning Objective

• Describe the impact of elevated Phe on long-term patient outcomes
KEY POINTS

1. High Phenylalanine (Phe) levels harm the brain

2. Traditional therapies do not completely protect individuals with PKU

3. Neuropsychological follow-up is important in identifying deficits associated with even well-treated PKU
KEY POINT #1

High Phenylalanine (Phe) levels harm the brain.

1. Evidence
2. Dopamine hypothesis
3. White matter hypothesis
Blood Phe and IQ Are Correlated in Individuals With PKU

<table>
<thead>
<tr>
<th>Observation period</th>
<th>Correlation between blood Phe and IQ</th>
<th>Lifetime IQ loss for each 100 µmol/L (1.6 mg/dL) increase in blood Phe (IQ points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical period (0–12 years old)</td>
<td>r = -0.35*</td>
<td>1.3–3.1</td>
</tr>
<tr>
<td>Lifetime (all ages)</td>
<td>r = -0.34*</td>
<td>1.9–4.1</td>
</tr>
</tbody>
</table>

* $P < 0.05$
Outcomes for Adults with PKU Are Worse if Discontinue Diet

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Discontinued Diet</th>
<th>Continued Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Problems</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

Prefrontal Cortex Is Sensitive to Reductions in Dopamine

Periphery (mostly liver)

Blood Brain Barrier

Brain

Phenylalanine → Tyrosine → L-DOPA → Dopamine

PAH = phenylalanine hydroxylase
BH4 = tetrahydrobiopterin
TH = tyrosine hydroxylase
AADC = aromatic amino acid decarboxylase

Dopamine pathways

White Matter

Myelin insulates axons to increase speed of neural signal transmission

Image from: RC McKinstry Washington University Mallinckrodt Institute of Radiology

KEY POINT #2

Traditional therapies do not completely protect individuals with PKU.

1. Adherence
2. Cognitive abilities
3. School achievement
4. Executive functioning
5. Processing speed
6. Emotional issues
Adherence to Diet Is Difficult

- ~1 in 3 children less than 10 years of age have blood Phe above recommended range
- Noncompliance increases in adolescence

Children with PKU on Diet Are at Risk for Lowered IQ

- Blood Phe and IQ are correlated  
  Waisbren et al 2007
- Variability in Blood Phe may be important  
  Anastasoaie et al 2008

Children with PKU on Diet Present More School Problems than Unaffected Peers

Executive Functioning Deficits

• We don’t know if he’s missing or just lost under all that paper!

• Planning
• Organization
• Working memory
• Initiation
• Inhibition of usual response
• Cognitive flexibility
Executive Deficits Across the Lifespan that May Worsen with Age

Summary Memory Score

Age (years)

Control
PKU

White et al 2001


Executive Deficits Make Diet Adherence Difficult

- Planning diet
- Remembering Phe intake for records
- Remembering to take formula
- Inhibiting impulse to eat foods not allowed on diet
- Maintaining medical food supplies
- Monitoring blood Phe and making appropriate adjustments in intake
Speed of Processing Is Reduced in Children with PKU

Adults with PKU Demonstrate Increase in Psychiatric Symptoms

*P* < 0.05 compared with 18-year-old controls

KEY POINT #3

Neuropsychological follow-up is important in identifying subtle deficits associated with even well treated PKU.

1. Case study
2. Screening by non-psychologists
3. The Genetics and Metabolism Psychology Network
Case Study: A.D.

History

• Male with PKU, now age 11 years
  – Newborn screening level 30 mg/dL
• Over-treated until 17 months
  – Failure to thrive and mild microcephaly
• Poor metabolic control from ages 2–4 years, until g-tube placed for intake of formula
• Levels varied until age 10 years
  – 3.6–16.9 mg/dL
• ADHD medication required
• IQ = 81 (100 is average)
Case Study

Recent and Current

• Began treatment with sapropterin at age 10
• Blood Phe steady at 5.4 mg/dL
• No longer needs ADHD medication
• Height 5th percentile; weight 2nd percentile
• IQ = 105 (Increase of 24 points)
Case Study

Current

- 11-year-old boy in 4\textsuperscript{th} grade
- Continues with g-tube
- Eczema and bedwetting
- Receives occupational therapy
- Has attention problems and requires one-on-one aide in classroom
- Kind, imaginative, eager to please
- Enjoys socializing, video games, sports
Assessment Observations

- Polite, cheerful, talkative
- Concentrated fairly well, but hummed as worked

Enjoyed relating facts about spiders

Told far-fetched stories about school and home, stating these capture interest of other children

- Did not appear to believe stories, but rather to intentionally elaborate
Intellectual Performance

Wechsler Abbreviated Scale of Intelligence (WASI)

WASI Score

Vocabulary
Matrix Reasoning
Full Scale IQ

Average
AD
Executive Functioning

• Example List
  - Carrot
  - Taxi
  - Elephant
  - Car
  - Airplane
  - Lettuce
  - Cat
  - Potato
  - Butterfly
  - Spinach
  - Boat
  - Tiger
  - Scooter
  - Squash
  - Parrot

California Verbal Learning Test

Trial 1: 4 words
Trial 5: 9 words
(Used categories)
Previous Year
Trial 1: 3 words
Trial 5: 5 words
Processing Speed

Example of a Symbol Search Task

€ £  € ≠ ¥ §  
¥ §  
YES
NO

∅ f √ ÷ ∏ ◊  
YES
NO
Wechsler Intelligence Scale for Children

Symbol Search

Coding

WISC-IV Subtest Score

Average

AD
Academic Achievement (WIAT)

Reading Recognition: 5th grade level
Reading increased 1 grade in last year

Numerical Operations: 3rd grade level
Careless errors, could not borrow or carry, did not attempt adding long columns of numbers
Math increased 1/2 grade in last year
Berry Visual Motor Integration Test (VMI): Standard Score = 70 (100 is average) Drew with confidence, but poor organization so details misplaced.

Same score as last year.
Recommendations

- Continue with extra help and occupational therapy
- Teach compensatory strategies in arithmetic
- Psychological counseling
- Behavioral therapy for weaning from g-tube
- Medical evaluation for eczema and bedwetting
- Re-evaluation in one year
<table>
<thead>
<tr>
<th>PSYCHOLOGICAL REALM</th>
<th>TEST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adaptive Functioning</td>
<td>Adaptive Behavior Assessment System (ABAS-II)</td>
</tr>
<tr>
<td>Behavior</td>
<td>Behavior Assessment System for Children (BASC-II)</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>Behavior Rating Inventory of Executive Function (BRIEF)</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)
Welcome to the Home Page of the Genetics and Metabolism Psychology Network (GMPN). We are a new organization with a vision!

This is an exciting time for the fields of genetics, metabolism, and psychology. With advances in identification and treatment of rare genetic and metabolic conditions comes a responsibility to add our voices to discussions regarding policy, research, and distribution of resources. The time has come for a Genetics and Metabolism Psychology Network so that we may take full advantage of our experiences and expertise.
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