Amino Acids and Amino Acidopathies: Phenylketonuria, Tyrosinemias, and Homocystinuria

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Some slides adapted from:

Thank you, Jean Marie Saudubrey, Mark Korson, Jerry Vockley and many others
How to recognise different types of trees from quite a long way away.
Amino acid metabolism
• Lateral chain R:
  – Carboxyl: Asp (β), Glu (γ)
  – Amine: Lys (ε), Orn (δ)
  – Hydroxyl: Thr, Ser, Tyr
  – Imidazole: His
  – Guanidinium: Arg
  – Thiol: Cys, Hcy
Protein metabolism (Adult 70 kg)

Proteins (~11 kg)

Proteolysis (~300 g/d)

Protein synthesis (~300 g/d)

Food intake

Free amino acids (~70 g/d)

Irreversible degradation (~70 g/d)

Specific functions

Denovo synthesis
triglycerides
  ↓ free fatty acids
  ↓ fatty acyl-CoA
  ↓ acylcarnitines
  ↓ β-oxidation
  ↓ ketones

glycogen
  ↓ G6P
  ↓ pyruvate
  ↓ lactate

PDH

TCA cycle
  ↓ reducing equivalents
  ↓ respiratory chain
  ↓ ATP

protein
  ↓ amino acids
  ↓ organic acids
  ↓ NH₄⁺

Urea cycle
  ↓ Urea

Courtesy of Dr. John Walter
Irreversible degradation

KETONE BODIES

Acetyl-CoA

Acetoacetyl-CoA

α-ketoglutarate

Phenylalanine
Tyrosine
Leucine
Lysine
Tryptophan

GLUCOSE

Phenylalanine
Tyrosine
Leucine
Lysine
Tryptophan

Arginine
Histidine
Glutamine
Proline

KETONE BODIES

Succinyl-CoA

α-ketoglutarate

Glutamate

Isoleucine
Methionine
Valine
Threonine

Oxaloacetate

Citrate

Malate

Aspartate
Asparagine

Pyruvate

Acetyl-CoA

Glx

Alanine
Threonine
Glycine
Serine
Cysteine

KETOGENIC and GLUCONEOGENIC amino acids

GLUCOSE

Phenylalanine
Tyrosine
Leucine
Lysine
Tryptophan

Arginine
Histidine
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Proline

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KETOGENIC and GLUCONEOGENIC amino acids

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Phenylalanine
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Glx

Alanine
Threonine
Glycine
Serine
Cysteine

KETOGENIC and GLUCONEOGENIC amino acids

GLUCOSE
Muscle amino acids

1 g N = 6.25 g protein = 30 g muscle

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>% of N</th>
<th>Recommended Intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu (MSUD)</td>
<td>8.5%</td>
<td>500-700</td>
</tr>
<tr>
<td>Val (MSUD)</td>
<td>5.5%</td>
<td>300-400</td>
</tr>
<tr>
<td>Ileu (MSUD)</td>
<td>5%</td>
<td>280-400</td>
</tr>
<tr>
<td>Phe (PKU)</td>
<td>4%</td>
<td>200-400</td>
</tr>
<tr>
<td>Meth (HSC)</td>
<td>2%</td>
<td>120-250</td>
</tr>
</tbody>
</table>

mgAA/gN (%/g N)
De novo amino acid synthesis

- Essential and non-essential amino acids
  - **Essential AA**: Inborn errors of AACatabolism
    - *Cannot* be synthesized by humans
    - *Must* come from food
  - **Non-essential AA**: Inborn errors of AAsynthesis
    - *Can* be synthesized by humans
    - Carbon skeletal comes from glucose and other amino acids
    - Nitrogen comes from other amino acids
# Amino acid classification

<table>
<thead>
<tr>
<th>Essential</th>
<th>Non-essential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threonine</td>
<td>Alanine</td>
</tr>
<tr>
<td>Valine</td>
<td>Asparagine</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>Aspartate</td>
</tr>
<tr>
<td>Leucine</td>
<td>Cysteine</td>
</tr>
<tr>
<td>Methionine</td>
<td>Glutamate</td>
</tr>
<tr>
<td>(Cysteine)</td>
<td>Glutamine</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Glycine</td>
</tr>
<tr>
<td>(Tyrosine)</td>
<td>Hydroxyproline</td>
</tr>
<tr>
<td>Lysine</td>
<td>Hydroxylysine</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Proline</td>
</tr>
<tr>
<td>Histidine</td>
<td>Serine</td>
</tr>
<tr>
<td>Arginine</td>
<td>Tyrosine</td>
</tr>
</tbody>
</table>
Protein catabolism

- Muscle protein content is 20 g%
- Nitrogen protein content is 16%
- 1 g nitrogen = 6.25 g protein = 30 g muscle
- Amino acid composition of proteins is genetically determined (doesn’t depend on the diet)
- In catabolic situations amino acids released from muscles are oxidized and nitrogen is converted to urea
Catabolism in control and PKU

CONTROL
Muscle 100 g
Protein 20 g

20 AA
3.2 N

Leu, Ile, Phe...
186 mmol

CO₂+H₂O
UREA (100 mmol)

PKU
Muscle 100 g
Protein 20 g

19 AA
PHE (4%)

(Leu, Ile...)
800 mg
(186 mmol)

3.2 g N

CO₂+H₂O
UREA (100 mmol)
Nitrogen excretion

- Relationship between urinary urea nitrogen excretion and body surface area
Food intake

• Feeding → exogenous proteins
  – Digestion → free amino acids and peptides (di- and tri-)
  – Essential and non-essential amino acids
  – Allows endogenous protein synthesis

• Defective intake
  – Kwashiorkor: protein-only deficit
  – Marasmus: combined deficit of protein and calories
Amino acidopathies

Majority can be identified by newborn screening
Hyperphenylalaninemia

• “Classic” phenylketonuria
  – untreated phe >1200 µmol/L
• “mild PKU”
  – untreated phe 600-1200 µmol/L
• Hyperphenylalaninemia
  – untreated phe < 600 µmol/L when well
Phenylalanine hydroxylase (PAH) is a key enzyme in the metabolism of phenylalanine to tyrosine. It requires BH₄ (biopterin) as a cofactor. BH₄ is also a cofactor for tyrosine hydroxylase (dopamine synthesis) and tryptophan hydroxylase (serotonin synthesis). The reaction involves several other enzymes including DHPR, PCD, GTPCH, GTP, SR, and PTPS.
Phenylketonuria (PKU)

- Liver phenylalanine hydroxylase (PAH) deficiency
- Autosomal recessive inheritance
- Incidence ~1:16,000 live births in the US

- Homotetramer ("dimer of dimers")
- Allosteric activation
  - confirmation determines enzyme activity
  - Phe activates enzymatically favorable conformation
  - BH4 stabilizes tetramer, but supports lower activity confirmation
Other causes of hyperphe

• Rare variants of biopterin synthesis or recycling (about 1% of severe hyperphe)
  – GTP cyclohydrolase
  – Dihydropteroptidne reductase
  – 6-pyruvoyl-tetrahydropterin synthase
    • All 3 generally more difficult to treat, require BH4 and usually dopa
  – Pterin-alpha-carbinolamine dehydratase
    • Generally mild, excrete 7-biopterin

• Hyperphe, not BH4 deficient
  – DNAJC12 – molecular chaperone for the hydroxylases – PAH, TH and TPH
Untreated PKU

• “Normal” development for 6–9 months, feeds well
• 9–12 months signs of slowing in developmental progress, head growth slows
• About 1 year clearly developmentally delayed, light hair, eczema, musty odor of “mouse urine”, may have seizures

• Severe intellectual disability with behavior problems — eventual institutionalization
• White matter hyperintensities – “pseudoleukodystrophy”
Pathophysiology

- Elevated total body phenylalanine
- Excessive phe in the brain
- Reduced large neutral amino acid transport into the brain (including tyrosine and tryptophan)
- Reduced synthesis of key neurotransmitters (e.g., dopamine, serotonin), especially during development
  - Mouse data suggests inhibition by CNS Phe of TH and TPH2 activity
- No direct pathologic effect on the liver known
Therapy

• Dietary phe reduction
• Competitive – large neutral amino acids supplements
• Chaperone therapy – sapropterin
• Enzyme substitution therapy – pegvaliase

Experimental
• Gut biome manipulation of absorption
• Gene correction or replacement therapy
Diet therapy

• Restrict dietary protein
• Phenylalanine intake: ~250-350 mg/day in classical form
  – Breastfeeding often manageable
• Supplement with phenylalanine-free medical food to guarantee the daily requirements
  – Non-offending amino acids
  – Glycomacropeptide – low phe casein product
  – Vitamins and minerals
  – Distribute through the day
• “Diet for life”
Strategies for breastfeeding

• Alternate feedings

• Mix in a bottle (breast milk provides intact protein in a traditional formula recipe)

• Bottle first with metabolic formula with each feed, followed by nursing (one breast for at least 10 min to access hindmilk)
Table 3
Guidelines for PHE, TYR, and protein intake for individuals with PKU.

<table>
<thead>
<tr>
<th>AGE</th>
<th>PHE&lt;sup&gt;a&lt;/sup&gt; (mg/day)</th>
<th>TYR&lt;sup&gt;a&lt;/sup&gt; (mg/day)</th>
<th>Protein&lt;sup&gt;b&lt;/sup&gt; (g/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants to &lt;4 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;3 months&lt;sup&gt;c&lt;/sup&gt;</td>
<td>130–430</td>
<td>1100–1300</td>
<td>2.5–3.0</td>
</tr>
<tr>
<td>3 to &lt;6 months</td>
<td>135–400</td>
<td>1400–2100</td>
<td>2.0–3.0</td>
</tr>
<tr>
<td>6 to &lt;9 months</td>
<td>145–370</td>
<td>2500–3000</td>
<td>2.0–2.5</td>
</tr>
<tr>
<td>9 to &lt;12 months</td>
<td>135–330</td>
<td>2500–3000</td>
<td>2.0–2.5</td>
</tr>
<tr>
<td>1 to &lt;4 years&lt;sup&gt;d&lt;/sup&gt;</td>
<td>200–320</td>
<td>2800–3500</td>
<td>1.5–2.1</td>
</tr>
<tr>
<td>After early childhood&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4 years to adult</td>
<td>200–1100</td>
<td>4000–6000</td>
<td>120–140% DRI for age&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pregnancy and lactation&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimester 1</td>
<td>265–770</td>
<td>6000–7600</td>
<td>≥70</td>
</tr>
<tr>
<td>Trimester 2</td>
<td>400–1650</td>
<td>6000–7600</td>
<td>≥70</td>
</tr>
<tr>
<td>Trimester 3</td>
<td>700–2275</td>
<td>6000–7600</td>
<td>≥70</td>
</tr>
<tr>
<td>Lactation&lt;sup&gt;h&lt;/sup&gt;</td>
<td>700–2275</td>
<td>6000–7600</td>
<td>≥70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from Acosta [118], recommendations for PHE and TYR intake for infants and children <4 years with more severe PKU and treated with PHE-restricted diet alone. TYR intake recommendations may require adjustment based on blood TYR monitoring.
Monitoring diet therapy

• Provide adequate calories
• Provide adequate protein, vitamins, minerals
• Maintain normal growth and development
• Monitor blood Phe and Tyr
• Monitor other parameters (development, psychological status, bone density)
  – Consider monitoring iron and Vitamin D from time to time
Other therapies

Goal to enhance phe tolerance and normalize diet

- **Sapropterin**
  - 20mg/kg/day
  - Infant – 24 hour trial >30% reduction in phe (with stable or no diet treatment)
  - Older 48 hours to 30 days trial
  - May have gradual onset
  - Requires some protein to work (null alleles unaffected)
Some sapropterin responsive mutations

<table>
<thead>
<tr>
<th>cDNA</th>
<th>Protein</th>
<th>Cases in PAHdb</th>
<th>Responsive to Sapropterin</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1222C&gt;T</td>
<td>p.Arg408Trp</td>
<td>6.7%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>c.1066-11G&gt;A (IVS10-11G&gt;A)</td>
<td>p.Ile65Thr</td>
<td>5.3%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>c.194T&gt;C</td>
<td>p.Ile65Thr</td>
<td>4.1%</td>
<td>89%</td>
</tr>
<tr>
<td>c.782G&gt;A</td>
<td>p.Arg261Gln</td>
<td>3.6%</td>
<td>78%</td>
</tr>
<tr>
<td>c.842C&gt;T</td>
<td>p.Pro281Leu</td>
<td>2.9%</td>
<td>None [Leuders et al 2014, biopku.org]</td>
</tr>
<tr>
<td>c.1315+1G&gt;A (IVS12+1G&gt;A)</td>
<td>p.Arg158Gln</td>
<td>2.8%</td>
<td>12.5% [biopku.org]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None [Leuders et al 2014]</td>
</tr>
</tbody>
</table>

Data obtained from: PAHdb accessed 5/8/2016 (biopku.org); and Leuders et al [2014]. All changes with >2.5% frequency in the PAHdb database were included. In database searches, homozygosity was assumed for calculations; however, this is a rare finding in consanguineous individuals. It is recommended that all affected individuals be tested for personal responsiveness. Genetic changes shown affect >2.5% of the database population. See biopku.org for the most up-to-date information and additional references.
Other therapies

Goal to enhance phe tolerance and normalize diet

• Pegvaliase
  – Plant enzyme – phenylalanine ammonia lyase
  – Does not reduce need for tyrosine
  – Immunologic reactions must be managed
  – Titrate dose to keep phe in physiological range on normal diet
  – Not recommended during pregnancy
  – FDA approval for 16 years and up
“Maternal” PKU

- Phenylalanine teratogenicity
- microcephaly,
- congenital cardiac lesion
- Intellectual disability
“Maternal” PKU Management

• Ideally start aggressive therapy before pregnancy
• Phe in target range as early as possible for unplanned pregnancy
• Often need aggressive Tyr supplements, especially 3rd trimester
• Sapropterin seems safe
• Risk of high phe likely outweighs potential risk for use of sapropterin and consideration for pegvaliase
Universal lessons from PKU

• Screening and treatment can be effective
• NBS can uncover milder forms for which the need to treat may not be obvious
• Unanticipated future consequences, for example maternal PKU, may occur or be revealed
• Treatment/intervention creates a new “natural history”
• The pathogenesis is more complicated than you think
• Alternative therapies may be developed over time
Tyrosine catabolic pathway

Tyrosine amino transferase tyrosinemia type II

4-hydroxyphenylpyruvic dioxygenase tyrosinemia type III

4-hydroxyphenylpyruvate

Homogentisic acid

Maleylacetoacetate

Fumarylacetoacetate

Fumaric acid

Acetoacetic acid

Succinylacetone

Keratitis (eye)

Renal Fanconi syndrome

Porphyric crises

Aminolevulinic acid

Porphobilinogen

Liver and renal damage

Liver and renal damage

FAH

Fumarate

Acetoacetate

Succinate

Hereditary tyrosinemia type 1

PBG synthase

Succinylacetone*
Tyrosinemia type I

- Fumarylacetoacetate hydrolase deficiency
- Autosomal recessive inheritance
- Founder effect
  - Quebec, Canada
  - Finland
- 3 presenting forms:
  - Early in infancy (1 to 6 months): Liver disease (hepatic failure or cholestatic jaundice or cirrhosis with renal tubulopathy)
  - Late infancy: Rickets due to renal tubulopathy (Fanconi syndrome) with no obvious liver failure
  - Porphyria-like attack at any age (can be presenting sign)
Cellular effects tyrosinemia I

• Toxic compounds (don’t cause ”intoxication” symptoms)
  – Fumarylacetoacetate, maleylacetoacetate
  – Succinylacetone

• Hepatocellular damage
  – Cirrhosis
  – Hepatocellular carcinoma
  – High alpha fetoprotein

• Renal tubule damage
  – Renal Fanconi syndrome
  – Hypophosphatemic rickets
Succinylacetone

• Succinylacetone inhibits
  – \( \Delta \)-aminolevulinic acid dehydratase activity
    • Porphyria-like abdominal pain crises
    • Peripheral neuropathy
  – 4-hydroxyphenylpyruvic dioxygenase
    • Tyr III enzyme defect, target of NTBC
Treatment

• 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexane-dione (NTBC)
  – Inhibits 4-hydroxyphenylpyruvic acid dioxygenase
  – Further increases plasma tyrosine
  – Decreased production of FAA and succinylacetone
  – Markedly reduces, but may not eliminate, hepatocellular carcinoma

• Phenylalanine and tyrosine restriction to avoid excessive hypertyrosinemia
  • risk of neurodevelopmental issues and keratitis)

• Liver transplant if hepatocellular carcinoma develops
Monitoring

- Therapeutic response to nitisinone
  - Plasma drug concentrations >35 µmol/L inhibit enzyme 99.9%
  - Some also monitor plasma succinylacetone to see complete suppression (plasma SA normal)
  - Start nitisinone at 1 mg/kg/day (usually divided BID for first year)
  - Titrate dose to desired plasma concentration and/or suppression of SA

- Dietary restriction of Phe and Tyr to keep plasma tyr <600 µmol/L

- Dried blood spot testing including SA, nitisone concentration, tyr and phe is available but drug concentrations may not correlate well with plasma
Other defects in the tyrosine catabolic pathway

Plasma metabolites (amino acids)
- Tyrosine
- Phenylalanine

Urine metabolites (organic acids)
- 4-hydroxyphenylpyruvate,
- 4-hydroxyphenyllactate
- 4-hydroxyphenylacetate
Other tyrosinemias

Type II – tyrosine aminotransferase
• AKA Richner Hanhart syndrome
• Incidence estimate <1:1X10⁶
• Clinical findings
  – Corneal crystals (~75%) – typically develop in first year of life, but may occur later
    – Photophobia
    – Pain
    – Tearing
    – Erythema/injection of sclera
  – Eventually leads to corneal clouding
  – Can be mistaken for herpetic or other viral infection early on, but does not respond to anti-viral therapy

https://disorders.eyes.arizona.edu/disorders/tyrosinemia-type-ii
Type II – tyrosine aminotransferase

• Clinical findings
  – Plantarpalmar hyperkeratosis (~80%)
    – Begin in first year to adult life
    – Can have pits
    – Often painful
    – Non-specific histology
  – Intellectual disability
    – Up to 60% of untreated
    – Typically apparent between 1-5 years of age
    – Treatment by 1 year of life appears to prevent intellectual decline

https://www.imagejournals.org/articles/tyrosinemia-type-presented-as-food-allergy-137.html
Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

• Incidence estimate <1:1X10^6

• Ocular findings not reported
  • But has been reported in anecdotally in patients with HPPD deficiency due to NTBC treatment

• Skin findings not reported as in type II
  • But has been reported in anecdotally in patients with HPPD deficiency due to NTBC treatment
Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

- Autosomal dominant form called Hawkinsinuria -- benign
Type III – 4-hydroxyphenylpyruvic acid dioxygenase deficiency (enzyme inhibited by NTBC)

• Intellectual disability reported in late diagnosed patients
  – Question of several treated patients also having mild developmental abnormalities?
  – Seizures reported (but several case reports from consanguineous relationships, so relationship not entirely clear
  – Anecdotal reports of untreated adults with “normal” development
  – Some developmental abnormalities reported in patients identified by NBS who had less than recommended tyrosine control
    – Is there a role of CNS down-stream metabolites
    – Are there toxicities of phenolic metabolites
Other tyrosinemias

Treatment

- Restriction of dietary tyrosine and phenylalanine
- Goals based on empiric observation and practical issues (i.e., no data)
  - Plasma tyr <600
  - Plasma phe near normal range
- Regular eye exams and skin checks
- Monitor neurodevelopment
Transient tyrosinemia of the newborn

- **Cause** – purported to be due “immature” enzymes, particularly HPPD, the product of which may also inactivate the enzyme.

- **Clinical**
  - Self limiting over 1 to 2 months
  - Apparently benign

- **Incidence** ~3-4:1,000
  - More common in premature infants

- **Older literature** suggests ascorbic acid (vitamin C) – 100 mg/day for 1-2 weeks – may speed up correction
Remethylation

Pathways of methionine metabolism

SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; THF, tetrahydrofolate; MeCbl, methylcobalamin.

1. cystathionine beta-synthase; 2. methionine adenosyltransferase I/III; 3. methionine adenosyltransferase II; 4. glycine N-methyltransferase; 5. numerous methyltransferases; 6. S-adenosylhomocysteine hydrolase; 7. methionine synthase; 8. betainehomocysteine methyltransferase; 9. Serine hydroxymethyltransferase; 10. methylenetetrahydrofolate reductase; 11. cystathionine gamma-lyase

Transulfuration
Disulfide bonds

Methionine

\[
\text{NH}_2-\text{CH}-\text{COOH} \quad \text{Normal Plasma Concentration}
\]

\[
\text{CH}_2 \\
\text{CH}_2 \\
\text{S} \\
\text{CH}_3
\]

10-35\mu M

Homocysteine

\[
\text{NH}_2-\text{CH}-\text{COOH} \quad \text{Undetectable in normal plasma}
\]

\[
\text{CH}_2 \\
\text{CH}_2 \\
\text{SH}
\]

5-15\mu M in plasma treated with a reducing agent

Homocystine

\[
\text{NH}_2-\text{CH}-\text{COOH} \quad \text{Undetectable}
\]

\[
\text{CH}_2 \\
\text{CH}_2 \\
\text{S} \\
\text{CH}_2 \\
\text{S} \\
\text{CH}_2 \\
\text{NH}_2-\text{CH}-\text{COOH}
\]
Elevated MET: caveats

• When accurate homocysteine measurements are important, measure “total homocysteine” and don’t rely on amino acid analysis, unless:
  – You can make sure the specimen gets to the lab quickly, and…
  – The specimen will be deproteinized soon after arrival in the laboratory

• Total homocysteine in this case measured 150 µM
Classical homocystinuria

- Cystathionine β-synthase deficiency
- Autosomal recessive inheritance
- Incidence = 1/200,000 to 1/400,000 births
  - Incomplete ascertainment
  - Cases often missed on newborn screens obtained during the first week of life
- 50% of CBS mutations are pyridoxine (vitamin B<sub>6</sub>) responsive
Classical untreated homocystinuria

- Skeletal malformations
  - Marfanoid habitus
  - Osteoporosis
  - Scoliosis
  - Most common in B$_6$ non-responsive forms
Other clinical findings

• Eye abnormalities
  – Ectopia lentis
    • 90% of affected individuals
    • Often bilateral
    • Typically down and toward nose (opposite of Marfan)
  – Myopia
  – May be an isolated presenting sign in children or adults

• Developmental disability and neuropsychiatric symptoms in many, but not all
Recurrent thromboembolism

- May be a isolated presenting sign in late-onset B<sub>6</sub> responsive forms
- Thromboembolism can be a presenting sign
  - Phlebitis
  - Pulmonary embolism
  - Cerebrovascular accident
- Environmental triggers
  - Anesthesia
  - Catabolism
  - Smoking
  - Oral contraceptives
Atherosclerotic disease
Thrombosis

Homocystinuria

Thrombus in popliteal vein

Note the collateral circulation
Thromboembolic stroke

Courtesy JM Saudubray
Other causes of homocystinuria

- Methionine Transamination Metabolites (TAM)
- S-Adenosyl-Methionine (adoMet)
- Methyl Acceptors
  - Guanidinoacetate
  - Protein
  - Lipids
  - DNA, RNA
  - Others
- Homocysteine
  - Cystathionine
    - B-synthase
    - B6
  - Cysteine
  - S04
- Serine
- Betaine
  - Methionine synthase
  - B12
  - Methylcobalamin
- Dimethylglycine
- Tetrahydrofolate (THF)
  - 5, 10-Methylene THF
  - 5,10-methylene THF reductase
  - S-Methyl THF
- Cytosol
- Protein
- Adenosyl Methionine (AdoMet)

Therapy (CBS deficiency)

- Pyridoxine responsiveness – 10 mg/kg/day (max. 500 mg)
  - Test total Hcy 2-3 X before Rx and 2-3 X on Rx after 4-6 weeks
  - >20% decrease is considered responsive (starting above 50 µmol/L)
  - High dose pyridoxine (>900 mg) can cause peripheral neuropathy
- Folate for all, B12 if deficient
  - HCU formulas usually have plenty of both
- Diet therapy – low protein, low-met formula
- Betaine – start at 50-100 mg/kg/day divided BID
  - Can increase up to 200 mg/kg/day, rarely benefit to higher dose
  - BHMT is saturable enzyme, so demonstrating additional benefit on plasma Hcy is helpful for higher doses
Methionineadenosyltransferase I/III (Mat I/III) Deficiency

- Rare defect in conversion of methionine to s-adenosylmethionine
- SAM is an important methyl donor in a variety of pathways

Clinical
- Not clear whether there are clinical implications or not
- SAM deficiency vs. excess met

Treatment
- Limiting met may lead to worse inadequacy of SAM
- Excessive met may cause increased intracranial pressure
- Consider both?
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