Disorders of amino acid metabolism

http://plantandsoil.unl.edu/croptechology2005/UserFiles/Image/siteImages/AminoAcidLG.gif
General comments on AA metabolism
Disorders of aromatic AA metabolism
Disorders of branched chain AA metabolism
Disorders of sulfur metabolism
Disorders of propionate, B12 and biotin metabolism
Urea cycle disorders
Other disorders of AA metabolism and defects in creatine synthesis
Exam questions

- Disorders or aromatic and branched-chain amino-acids
- Urea cycle disorders
- Dietary and genetic disorders of folate, cobalamine, and sulfur amino acid metabolism
- Disorders of amino acid metabolism and of creatine synthesis.
- Dietary protein: 80 g
- Body protein: (~10 kg)
- Body protein efflux: ~400 g
- Enzymes, intestinal cells, mucus: 70 g
- Amino acids and dipeptides
- Amino acids
- Metabolites
- Urine: (70 g)
- Faecal loss: (10 g)

http://uk.geocities.com/david.bender@btinternet.com/images/proteinoverview.png
## Energy stores

<table>
<thead>
<tr>
<th>Energy store</th>
<th>tissue</th>
<th>amount (g)</th>
<th>energy (kj)</th>
<th>(kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycogen</td>
<td>liver</td>
<td>70</td>
<td>1176</td>
<td>280</td>
</tr>
<tr>
<td>Glycogen</td>
<td>muscle</td>
<td>120</td>
<td>2016</td>
<td>480</td>
</tr>
<tr>
<td>Glucose</td>
<td>blood</td>
<td>20</td>
<td>336</td>
<td>80</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>fat</td>
<td>15 000</td>
<td>567 000</td>
<td>135 000</td>
</tr>
<tr>
<td>Proteins</td>
<td>muscle</td>
<td>6000</td>
<td>100 800</td>
<td>24 000</td>
</tr>
</tbody>
</table>
Amino Acid Metabolism

% of total

0  10  20  30

Liver

Glucose

Urea

-NH₂

Pyruvate

Gut

Kidney

Alanine

Glutamine

Glycine

Other glucogenic amino acids

Muscle

Brain and other tissues

Brain and other tissues

Glucose

Phospho-enol pyruvate

Pyruvate

Acetyl CoA ↔ Acetoacetyl CoA

Asparagine
Aspartate

Phenylalanine
Tyrosine

Isoleucine
Methionine
Valine

Oxaloacetate

Fumarate

Succinyl-CoA

α-Keto-glutarate

Arginine
Glutamate
Glutamine
Histidine
Proline
Protein requirements

Protein intake
How To Achieve A Positive Nitrogen Balance And Why You Care

By Fitness Atlantic Writer: Mike Westerdal
Patients with disorders of AA metabolism

incidence of aminoaciopathies for ČR ~ 1:3000
~ 20 patients with HPA/PKU
~ 30 patients with other AA/OAU

ČR, 2005, n=127
Patophysiology IEM

substrate

<1500 Da
Aminoacidopathies - most common mechanisms

- Accumulation of AA
- Ammonia accumulation
- Carbon skeleton accumulations - organic acids
- Product deficiency
Organic acidurias

- several dozens of small molecule diseases
- common feature: excretion of carboxylic acids (test-organic acids in urine)
- originin usually from carbon skeleton degradation of AAs (or saccharides or lipids)
- usually acute presentation- „intoxication type“
- metabolic acidosis common (combination with hyperammonenemia frequent)
Disorders of aromatic amino acid metabolism
The image depicts a metabolic pathway leading to the production of phenylalanine (PAH). The pathway starts with tyrosine, which is converted to p-hydroxyphenylpyruvate by tyrosine-transaminase. This is then converted to homogentisate by p-hydroxyphenylpyruvate-dioxygenase. Homogentisate is further converted to 4-fumarylacetoacetate by homogentisate-dioxygenase. 4-Fumarylacetoacetate is then converted to 4-maleylacetoacetate by 4-fumarylacetoacetate-cis-trans-isomerase. This is a key step in the metabolism of tyrosine and phenylalanine, and it plays a crucial role in the biosynthesis of aromatic compounds.

For more information, visit the following website: http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Phenylketonuria

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Mutations in *PAH* gene

zdroj: PAH mutation database
Metabolic Pathways of Phenylalanine

- Phenylalanine
- Phenylpyruvic acid
- Tyrosine
5,6,7,8-Tetrahydrobiopterin

\[
\text{H}_4\text{-Biopterin (BH}_4\text{)} \quad \text{H}_2\text{-Biopterin (qBH}_2\text{)}
\]

\[
\text{Phenylalanine hydroxylase}
\]

\[
\text{Dihydropteridinede reductase}
\]

\[
\text{NADP}^+ \quad \text{NADPH} + \text{H}^+
\]
Aromatic Amino Acid Hydroxylases and Function of Tetrahydrobiopterin

Guanosine triphosphate (GTP) → \( \text{GIPCH} \) → Dihydروneopterin triphosphate → \( \text{PTPS} \) → 6-Pyruvoyl-tetrahydropterin → \( \text{SR} \) → Tetrahydrobiopterin

\( \text{DHPR} \) → q-Dihydrobiopterin → \( \text{PCD} \) → Pterin-4a-carbinolamine → Biopterin

Phenylalanine → Tyrosine → L-DOPA → Dopamine

Tyrosine → 5-OH-Tryptophan → Serotonin

Tryptophan

Dopamine

HVA

5HIAA

\( \text{Arg} \) → Cit + NO·

http://www.bh4.org/biodefimages/Fig_bh4biox.gif
Untreated HPA/PKU

- CZ 1:6,500, Turkey 1:3,000, very rare Finland, N Europe 1:15,000
- 1-2% HPA secondary due to primary pterine defects
- 30% patients BH4 sensitive
- newborn screening
- untreated HPA- mental retardation, typical mouse odour, light complexions, eczema, epilepsy
- maternal HPA-VCC, microcephaly a PMR
Classical dietary treatment of PKU

Prof. Horst Bickel

http://www.milupa-metabolics.com/produkte.php?sourceId=162&sysId=139
PKU- 3rd d

http://www.pahdb.mcgill.ca/images/pku.gif&imgrefurl

PKU- 12the mo
Tyrosine

Tyrosinemia type 2

hyperkeratossi herpetiformic keratitis

http://www.ijo.in/articles/2007/55/1/images/IndianJOphthalmol_2007_55_1_57_29497_2.jpg
http://208.96.47.3/images/community/dermatlas/Tyrosinemia_type_2_2_041213.png
Tyrosinemia type 2

- very rare
- herpetiformic keratitis
- palmoplantar hyperkeratoses with ulcers
- PMR, growth retardation
- dietary treatment
PAH

Alkaptonuria

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Coxarthrosis
Valvular involvement
Urolithiasis

Harwa, 1500 př.n.l.
Alkaptonuria treatment-artifical block above the enzyme block

nitison (NTBC)

? what are the possible therapy complications?
Tyrosinemia 1

Tyrosine $\xrightarrow{\text{Tyrosine-transaminase}}$ p-Hydroxyphenylpyruvate $\xrightarrow{\text{p-Hydroxylphenylpyruvate-dioxygenase}}$ Homogentisate

- Tyrosine
- p-Hydroxyphenylpyruvate
- Homogentisate

4-Fumarilacetoacetate

Acetoacetate $\xrightarrow{\text{4-Fumarylacetocatase}}$ Maleylacetocatate $\xrightarrow{\text{cis-trans-isomerase}}$ 4-Maleylacetocatate

Fumarate

http://www.chemie.fu-berlin.de/chemistry/bio/aminoacid/gif/phe.gif
Tyrosinemia type I

- Fumarylacetoacetase deficiency
- Acute manifestation in infancy
- Hepatorenal involvement with acute hepatic dysfunction and Fanconi syndrome
- Porphyric crises - abdominal cramps
- Chronic - ci heatsis and ca in cirhosim
- Diet, nitisone, liver transplant
Tyrosinemia type I
Alkaptonuria a tyrosinemia 1 treatment

nitison (NTBC)

http://www.natuurlijkerwijs.com/english/b4f4ca00.gif
Disorders of branched chain amino acids
BCAA

Valine

Leucine

Isoleucine

http://www.agron.iastate.edu/courses/Agron317/Images/Branched_chain_aa.jpg
Leucinosis/maple syrup urine disease

http://www.childrenshospital.org/newenglandconsortium/NBS/MSUD/MSUD1.jpg
MSUD

- Peracute presentation in newborns, intermittent variants
- Coma, dystonia-boxing, cycling
- Maple syrup odour
- Acute crisis prevention and management
- Long term treatment-diet

http://losyoruguas.com/archivos/0686.gif
Psychomotor development-MSUD

![Graph showing IQ averages and standard deviations for different age groups with symptoms or no symptoms.](Image)
Isovaleric acidemia

Isovaleric aciduria

- IVA-CoA DH deficiency
- Peracute/intermittent course
- Coma with acidosis/ketonuria, sweaty feet odour
- Acute crisis-elimination
- Long term-diet, karnitine, glycine
- Newborn screening

Disorders of sulfur amino acid metabolism
Methionine cycle

- Methionine cycle
- S-AdoMet → MG
- S-AdoHcy
- THF
- Methionine
- DMG
- Betaine
- Homocysteine
- Cystathionine
- Cysteinesulfinic acid
- Hypotaurine
- Taurine
- H₂S
- Cysteine
- L-gamma-glutamylcysteine
- CysGly
- Glutathione
- H₂SO₃⁻ → H₂SO₄⁻
Vitamins and Hcy metabolism

- AdoMet
- AdoHcy
- Homocysteine
- Cystathionine
- Cysteine
- THF
- Methionine
- DMG
- Betaine
- Cysteinesulfinate
- Hypotaurine
- Taurine
- L-gamma-glutamylcysteine
- CysGly
- Ser
- Gly
- THF
- Methyl-THF
- Methylene-THF
- H₂S
- Cysteine
- Glutathione

- Folates
- B12
- B2
- B6

- SO₃²⁻ → SO₄²⁻
CBS deficiency

- frequency 1:6.000-1:900.000
- classical and mild forms
- clinical triade
  - Connective tissue: marfanoid features, kyfoskoliosis, osteoporosis, lens luxation
  - hemokoagulation: thromboses
  - CNS: cognitive impairment, seizures

- therapy: low Met diet, pyridoxine as a chaperone, betaine to enhance remethylation
Remethylation homocystinurias

- About 10 diseases
- Low Met a low SAM
- Severely impaired myelinization
- Neurological sequelae
- Thrombosis
- Therapy- betaine, Met, SAM
Cystine
1810 Wollaston- bladder stone (Greek cystos)- „cystic oxid“

1817 Marcet- the same compound also found in kidney stones, family occurrence (2 sibpairs)
cystine
History of cystinuria

- 1908 Garrod - one of 5 IEMs
- incidence cca 1: 10 000
- 1994 SLCA1 gene, 1999 SLC7A9
- hundreds of mutations
- treatment: fluid intake, penicillamine, thiopronine
Aim of treatment = increased solubility

Cys-Cys

merkaptopropionylglycine (thiopronine)

4-5 L fluids/day alkalinization
Cystinosis

Chemiosmotic coupling between cystinosin and the lysosomal H⁺-ATPase.

- defect of lysosomal transporter cystinosin
- infantile form: Fanconi syndrome-severe tubulopathy
- FTT
- adultní forms: ocular involvement myopathy, hypothyreosis
- Rx- cysteamine locally and systematically
Disorders of propionate, cobalamin, folate and biotin metabolism
Folic acid and derivatives

6-Methylpteridin

>p-Aminobenzoic acid (PABA) Glutamic acid

Pteroylglutamic acid (Folic acid)

http://www.fao.org/docrep/004/y2809e/y2809e06.gif
Origin and daily requirements

Plant synthesis

- Daily folate requirements (µg/d, FAO)
  - Infants: 60
  - Children: 160-300
  - Adults: 400
  - Pregnancy: 600

http://www.hos.ufl.edu/meteng/HansonWebpagecontents/FolateTransport_clip_image002.gif
Transport and metabolism of folates
Transport and metabolism of folates

www.nature.com/.../v98/n9/thumbs/6604346f5th.jpg
http://www.ivis.org/images/advances/rc/chap03/fig4_xl.jpg  http://www.down-syndrome.org/uploads/2051/updates-2051-Fig1-600w.jpg
Primary defects

- **Rare conditions**
  - FolR1 deficiency
    - Autoantibodies against FolR1 (nongenetic)
  - PCFT deficiency (=hereditary folate malabsorption)
  - MTHFR deficiency

- **Clinical findings**
  - Neurological impairment: psychomotor retardation, seizures, hypomyelination, brain atrophy
  - Hematological findings: PCFT- megaloblastic anemia
  - Laboratory tests: normal S-folates in FolR1, hypogamaglobulinemia in PCFT, low csf folates in all defects
Folates and complex diseases

- **Epidemiological evidence**
  - Case control/prospective studies
  - Folate intake and/or folate concentration
  - Range of effects: OR/RR between ~0.3 and 1.0

- **Diseases studied**
  - NTD
  - Cancer
  - Atherosclerosis
  - Cognitive impairment/dementia

- **Etiology of low folate status**
  - Diet/ gastrointestinal problems
  - Genetics largely unknown
Vitamin B12

- complicated synthesis
- exogenous intake needed
- implied in only 2 reactions
- nutritional or endogenous deficiency is common
  - pregnancy and lactation
  - advanced age
  - GIT disorders
- long latent course
  - anemia
  - demyelinization
  - psychiatric manifestation
- treatment efficient and cheap

http://www.health-spy.com/hydroxob12.png
Resorpce kobalaminu
Intracellular B12 mtbl
Peritoneal dialysis in PA

http://www.metagene.de/program/d.prg?id_d=18
Propionic acidemia

- newborn variant: episodes of ketoacidosis/hyperammonemia, coma, pancytopenia
- milder forms - repeated encefalopathic crises, FTT
- chronic problems: FTT, infections, variable CNS involvement
- therapy: IMTV restriction, gut sterilization, biotin in some patients, aggressive treatment of crises, gastrostomy, liver transplant

http://www.uchsc.edu/cbs/images/fig2.JPG
Amino acids (~50%)
Odd-chained fatty acids (~30%)
Propionate (gut-flora derived) (~20%)
Other (small)

Propionyl-CoA → Propionyl-Carnitine

Propionyl-CoA Carboxylase

Biotin, ATP, HCO3

D-Methylmalonyl-CoA

D-Methylmalonyl-CoA Racemase

L-Methylmalonyl-CoA

Adenosylcobalamin, Methylmalonyl-CoA Mutase

MMA

D-Methylmalonyl-CoA Hydrolase

Succinyl-CoA

Krebs (TCA) Cycle

Energy
Amino acids
Glucose
Biosynthesis

Methylmalonic acidemia

- newborn variant: acute crisis with ketoacidosis, hyperammonemia and coma
- milder forms-repeated encephalopathic episodes
- chronic problems: nephropathy progressing in renal failure, variable CNS involvement (pacin picture partially deaf and mute), infections Candida sp.
- treatment: IMTV restriction, gut sterilization, in some patients B12, aggresivní treatment of acute episodes
Biotinidase deficiency

Biotinidase deficiency

- Various degree of BTD deficiency
- Impaired breakdown of biocytin and thus biotin incorporation
- Multiple carboxylase deficiency
- Eczema, seizures, PMR
- Miraculous response to biotin administration

http://www.rug.nl/umcg/faculteit/disciplinegroepen/ kindergeneeskunde/liverdigestivemetabolicdiseases/enzyme/images/ biotinidase-grafiek.jpg
Urea cycle disorders
Ammonia

- Ammonia cation
- Normal level 50-70 µmol/l
- Somnolence above cca 150 µmol/l
- Coma above 300-400 µmol/l
Hyperammonemia is a medical emergency.
# Urinary nitrogen excretion

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>g 24 h*</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>30</td>
<td>86</td>
</tr>
<tr>
<td>Ammonia ion</td>
<td>0.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0-1.8</td>
<td>4-5</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.5-1.0</td>
<td>2-3</td>
</tr>
</tbody>
</table>

Table 85-5 Estimation of the Incidence of Each Urea Cycle Disorder Based on Its Incidence Relative to Argininosuccinase Deficiency

<table>
<thead>
<tr>
<th>Enzyme Deficiency</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamyl phosphate synthetase</td>
<td>1 per 62,000</td>
</tr>
<tr>
<td>Ornithine transcarbamylase</td>
<td>1 per 14,000</td>
</tr>
<tr>
<td>Argininosuccinate synthetase</td>
<td>1 per 57,000</td>
</tr>
<tr>
<td>Argininosuccinase</td>
<td>1 per 70,000</td>
</tr>
<tr>
<td>Arginase</td>
<td>1 per 363,000</td>
</tr>
<tr>
<td>All urea cycle disorders</td>
<td>1 per 8200</td>
</tr>
</tbody>
</table>

OTC-clinical variability

Table 85-6 Distribution of Cases of Ornithine Transcarbamylase Deficiency

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal onset</td>
<td>134</td>
</tr>
<tr>
<td>Late onset</td>
<td>200</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td>&lt; 18 yr</td>
<td>61</td>
</tr>
<tr>
<td>&gt; 18 yr</td>
<td>5</td>
</tr>
<tr>
<td>Females</td>
<td></td>
</tr>
<tr>
<td>&lt; 18 yr</td>
<td>102</td>
</tr>
<tr>
<td>&gt; 18 yr</td>
<td>21</td>
</tr>
<tr>
<td>Unknown age</td>
<td>11</td>
</tr>
<tr>
<td>Total cases</td>
<td>334</td>
</tr>
</tbody>
</table>

Lethality of OTC

![Survival curve](image)

**Fig. 85-31** Long-term survival of 40 infants who survived their neonatal hyperammonemiac episode. Each small square represents length of time surviving patients were monitored (time until they were censored). Patients were censored at their age of orthotopic liver transplantation, when they were lost to follow-up, or when this study ended.
Scylla and Charibda
Other disorders of amino acid metabolism and creatine synthesis disorders
Glutaric aciduria type 1

Prolidase deficiency

- abnormal recycling of Pro into collagen
- urinary loss of iminodipeptides
- secondary immune defects
- ulcers and typical facial appearance
- PMR, splenomegaly, bone changes, mikrocytic anemia
- therapy local, systemic proline administration

http://dermatology.cdlib.org/127/case_presentations/prolidase/2.jpg
Hyperornithinemia

- OAT deficiency
- late onset 3rd-4th decade-night blindness
- gyrate atrophy of retina
- treatment with pyridoxine and dietary restriction of Orn

The retina of a patient with gyrate atrophy of the choroid and retina of the eye caused by ornithine aminotransferase (OAT) deficiency. [Image credit: Muriel Kaiser-Kupfer, NEI, NIH, Bethesda, MD, USA and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

Creatine metabolism
Enzymes:
AGAT = L-Arginine:glycine amidinotransferase
GAMT = S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase
IEMs in creatine biosynthesis and transport

- **GAMT deficiency (MIM 601240)** ~ 60 Pt *
  - 1994 (Stöckler et al)

- **AGAT deficiency (MIM 602360)** 7 Pt *
  - 2001 (Item et al)

- **CRTR deficiency (MIM 300036)** > 150 Pt *
  - 2001 (Salomons et al)

* 2008
**Biochemical and clinical findings**

<table>
<thead>
<tr>
<th></th>
<th>H-MRS</th>
<th>GAA U,P,CSF</th>
<th>CR U,P</th>
<th>CR/CRN U</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMT</td>
<td>Creat ↓↓</td>
<td>↑↑</td>
<td>↓</td>
<td>—</td>
</tr>
<tr>
<td>AGAT</td>
<td>↓↓</td>
<td>↓↓ n</td>
<td>(↓) n(U)</td>
<td>—</td>
</tr>
<tr>
<td>CRTR</td>
<td>↓↓</td>
<td>n</td>
<td>(↑)</td>
<td>↑*</td>
</tr>
</tbody>
</table>

- Clinical findings: developmental delay, various neurological problems, delayed speech, seizures
<table>
<thead>
<tr>
<th></th>
<th>deficiency correction</th>
<th>correction of accumulation</th>
<th>alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMT</td>
<td>supplement CR</td>
<td>restriction ARG</td>
<td>supplement ORN</td>
</tr>
<tr>
<td>AGAT</td>
<td>Supplement CR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CRTR</td>
<td>supplement CR, ARG</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>GLY*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoacidopathies-mechanisms

- Amino acid accumulation
- Ammonia accumulation
- Carbon skeleton accumulation - organic acids
- Product deficiency