Neurometabolic Disorders

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Outline

1. Urea cycle disorders
2. Fatty acid oxidation & carnitine disorders
3. Organic acidemias
4. Amino acidopathies
5. Peroxisomal disorders
6. Lysosomal disorders
7. Biogenic amine (neurotransmitter) disorders
8. Newborn screening
9. Summary table
Urea Cycle Disorders
Urea Cycle
Urea Cycle Disorders

• Inheritance
  – Autosomal recessive, except ornithine transcarbamylase deficiency (x-linked semi-dominant)

• Clinical presentation
  – Onset in neonatal period to 6th decade
  – Episodic hyperammonememic encephalopathy
    • altered mental status, headache, ataxia, seizures
    • nausea and vomiting
    • hyperventilation
  – Episodes provoked by illness, fasting, protein load, medications (eg. valproic acid)
  – Arginase deficiency: progressive spastic paraplegia, MR
14 mo F with ornithine transcarbamylase deficiency presenting with hyperammonemia
Urea Cycle Disorders

• General laboratory studies
  – Ammonia elevated > 80 umol/L (> 110 umol/L in neonate)
  – Primary respiratory alkalosis

• Plasma amino acids
  – Elevated glutamine
  – Abnormal citrulline, arginine, ornithine

• Urine organic acids
  – Orotic acid
  – Arginosuccinic acid
# Urea Cycle Disorders: plasma amino acids & urine organic acids

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Plasma amino acids</th>
<th>Urine organic acids</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylglutamate synthetase deficiency</td>
<td>Low citrulline</td>
<td>Low orotic acid</td>
</tr>
<tr>
<td>Carbamoyl phosphate synthetase deficiency</td>
<td>Low citrulline</td>
<td>Low orotic acid</td>
</tr>
<tr>
<td>Ornithine transcarbamylase deficiency</td>
<td>Low citrulline</td>
<td>High orotic acid</td>
</tr>
<tr>
<td>Arginosuccinate synthetase deficiency</td>
<td>High citrulline</td>
<td>High orotic acid</td>
</tr>
<tr>
<td>Arginosuccinate lyase deficiency</td>
<td>High citrulline</td>
<td>High orotic acid, arginosuccinic acid</td>
</tr>
<tr>
<td>Arginase deficiency</td>
<td>High arginine</td>
<td>High orotic acid</td>
</tr>
</tbody>
</table>
Urea Cycle Disorders: Treatment

• Acute
  – Stop protein
  – Provide protein-free calories via high dextrose infusion +/- intravenous lipid
  – IV ammonia scavenger Ammonul (sodium phenylacetate/benzoate)
  – IV arginine (except in arginase deficiency)
  – In severe/refractory cases, hemodialysis

• Chronic
  – Protein restriction
  – Oral ammonia scavengers, (Carbaglu in NAGS deficiency)
  – Oral L-citrulline/L-arginine (except in arginase deficiency)
  – Liver transplant in severe cases or if significant liver disease
Fatty Acid Oxidation & Carnitine Disorders
Mitochondrial Fatty Acid Oxidation

1. Long-chain Fatty Acid
2. Fatty Acid
3. Carnitine
4. CoA
5. Acyl-CoA
6. 3-hydroxyacyl-CoA
7. 2-enoacyl-CoA
8. 3-ketoacyl-CoA
9. Acyl-CoA
10. Acetyl-CoA
11. TCA Cycle
12. Acetyl-CoA (-2C) + Ketones
13. Dicarboxylic Acids

Plasma → Cytosol → Mitochondria

Glucose → Glucose-6-P
Fatty Acid Oxidation & Carnitine Disorders

- Fatty acid oxidation disorders
  - Short chain acyl-CoA dehydrogenase deficiency (SCADD)
  - Medium chain acyl-CoA dehydrogenase deficiency (MCADD)
  - Very long chain acyl-CoA dehydrogenase deficiency (VLCADD)
  - Short chain hydroxy-acyl CoA dehydrogenase (SCHADD)
  - Long chain hydroxyacyl-CoA dehydrogenase deficiency (LCHADD)
  - Mitochondrial Trifunctional Protein Deficiency (MTPD)

- Carnitine Disorders
  - Carnitine transporter deficiency
  - Carnitine palmitoyl-transferase 1 deficiency (CPT1)
  - Carnitine palmitoyl-transferase 2 deficiency (CPT2)
  - Carnitine-acylcarnitine translocase deficiency (CAT)

- Inheritance: autosomal recessive
Fatty Acid Oxidation & Carnitine Disorders

• Clinical presentation
  – Onset in neonatal period to adulthood
  – Episodes provoked by illness, fasting, high fat intake, medications
  – Hypoketotic hypoglycemia
  – Hepatopathy
  – SIDS, Reye-like syndrome
  – Long chain disorders:
    • Skeletal myopathy (episodic, exercise-induced)
    • Cardiomyopathy
    • Maternal HELLP syndrome or acute fatty liver of pregnancy
    • Retinopathy & axonal polyneuropathy (LCHAD/MTP)
Fatty Acid Oxidation & Carnitine Disorders: Investigations

• General laboratory studies
  – Hypoglycemia
    • inappropriately low plasma beta-hydroxybutyrate (BHB)
    • elevated free fatty acid/BHB ratio
  – Transaminitis (usually LFTs preserved)
  – Elevated CPK (1000’s)
  – Less common, acidosis and hyperammonemia

• Specialized metabolic studies
  – Plasma acylcarnitine profile
  – Free/total carnitine
  – Urine organic acids: dicarboxylic acids
  – Urine acylglycines
    • MCADD: phenylpropionylglycine, suberylglycine, hexanoylglycine
    • SCADD: ethylmalonic acid
# Plasma Acylcarnitines

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Plasma acylcarnitine abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatty acid oxidation disorders</strong></td>
<td></td>
</tr>
<tr>
<td>SCAD</td>
<td>C4</td>
</tr>
<tr>
<td>SCHAD</td>
<td>C4OH</td>
</tr>
<tr>
<td>MCAD</td>
<td>C8 &gt; C6 &gt; C10</td>
</tr>
<tr>
<td>VLCAD</td>
<td>C12, C14, C14:1, C16, C18</td>
</tr>
<tr>
<td>LCHAD</td>
<td>C14OH, C16OH, C18OH, C18:1OH</td>
</tr>
<tr>
<td>MTP</td>
<td>C14OH, C16OH, C18OH, C18:1OH</td>
</tr>
<tr>
<td><strong>Carnitine disorders</strong></td>
<td></td>
</tr>
<tr>
<td>CPT1</td>
<td>Decreased C16, C18, C18:1</td>
</tr>
<tr>
<td>CAT</td>
<td>C16, C18, C18:1</td>
</tr>
<tr>
<td>CPT2</td>
<td>C16, C18</td>
</tr>
</tbody>
</table>
Fatty Acid Oxidation & Carnitine Disorders: Treatment

• Acute
  – High dextrose infusion
  – MCT supplementation in long chain disorders

• Chronic
  – Avoidance of prolonged fasting (age dependent)
  – Carnitine supplementation if low
  – Long chain disorders
    • limit % calories from long chain fats (8-20%), monitor for essential fatty acid deficiency
    • MCT supplementation – GI side effects
    • Triheptanoin (investigational)
Organic Acidemias
Organic Acidemias

• *Classic organic acidemias*
  – Ketoacidosis, hyperammonemnia, neurological symptoms
  – eg. methylmalonic & propionic acidemia

• *Cerebral organic acidemias*
  – Neurological symptoms with no/minimal systemic metabolic abnormalities, macrocephaly in many
  – eg. glutaric acidemia type 1, L2-hydroxyglutaric acidemia, Canavan disease

• Inheritance: autosomal recessive

• Diagnosis: urine organic acids, plasma acylcarnitines

• MRI: many involve deep gray nuclei and subcortical U-fibres
Methylmalonic & Propionic Acidemia

• Disorders in pathway of branch chain amino acid oxidation

• Presentation
  – Episodic decompensations provoked by illness, fasting, high protein intake
  – Increased gap metabolic acidosis
  – Ketonemia/ketonuria*
  – Hyperammonemia
  – Hyper/hypoglycemia
  – Clinical: hyperventilation, altered mental status, seizure
  – Acute complications: metabolic stroke, pancreatitis
  – Chronic complications: Developmental delay, failure to thrive, movement disorder, diabetes, cytopenia
  – deafness & cardiomyopathy/long QT in propionic acidemia
  – optic atrophy & renal disease in methylmalonic acidemia
Methylmalonic & Propionic Acidemia

13 month old M with propionic acidemia

14 year old M with methylmalonic acidemia
Methylmalonic & Propionic Acidemia: Treatment

• Acute
  – Stop protein
  – High dextrose +/- lipid infusion
  – Base therapy if acidemic
  – L-carnitine if deficient
  – Methylmalonic acidemia may be B12 responsive

• Chronic
  – Protein restriction
  – May require chronic base therapy
  – L-carnitine
  – B12 therapy in methylmalonic acidemia if responsive
  – Liver transplant in severe cases
Glutaric Acidemia Type 1

- Disorder in lysine, hydroxylysine, tryptophan degradation pathway

- Presentation
  - Macrocephaly
  - Development initially normal
  - At risk for metabolic stroke during illness, especially in first 4 years of life
  - Following stroke, often severe disability with dystonia

- Treatment
  - Lysine and tryptophan restricted, arginine-enriched diet
  - If significant illness/high fever, restrict protein/lysine and increase calories
Glutaric Acidemia Type 1

5 year old M with glutaric aciduria type 1
Amino Acidopathies
Amino Acidopathies

• Heterogenous group of disorders, many associated with CNS involvement
  – Neurodevelopmental abnormalities
  – Acute CNS events (toxic, vascular)
  – Epilepsy

• All autosomal recessive

• Diagnosis
  – Plasma amino acids abnormal in many
  – Additional metabolic studies often required

• Many have specific & effective treatments
  – Maple syrup urine disease, homocysteinemias, PKU, tyrosinemia
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical features</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maple syrup urine disease</td>
<td>Cerebral edema, maple syrup odor</td>
<td>Elevated BCAA in plasma, elevated alpha-ketoacids in urine</td>
</tr>
<tr>
<td>Non-ketotic hyperglycinemia</td>
<td>Seizures (early myoclonic encephalopathy), myoclonus, hiccups, hypotonia, brainstem dysfunction</td>
<td>Elevated CSF/plasma glycine ratio (&gt;0.08)</td>
</tr>
<tr>
<td>Homocysteinemias</td>
<td>Demyelination, vascular stroke, marfanoid &amp; lens dislocation in CBS deficiency</td>
<td>Elevated total homocysteine, abnormal methionine, abnormal MMA in cobalamin disorders</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Developmental delay, autism, pale skin/eczema in untreated</td>
<td>Elevated phenylalanine, elevated phe/tyr ratio</td>
</tr>
<tr>
<td>Tyrosinemia type 1</td>
<td>Liver and renal disease, porphyric crises</td>
<td>Elevated tyrosine, elevated urine &amp; plasma succinylacetone</td>
</tr>
<tr>
<td>Sulfite oxidase/molybdenum cofactor deficiency</td>
<td>Mimics neonatal HIE after well period, epilepsy</td>
<td>Elevated urine sulfocysteine and urine sulfites, low urate (molybdenum cofactor deficiency)</td>
</tr>
<tr>
<td>Serine deficiency disorders</td>
<td>Epilepsy, congenital microcephaly, malformations</td>
<td>Low CSF serine</td>
</tr>
<tr>
<td>Asparagine synthetase deficiency</td>
<td>Epilepsy, congenital microcephaly, hyperekplexia</td>
<td>Low CSF asparagine</td>
</tr>
<tr>
<td>Glutamine synthetase deficiency</td>
<td>Hyperammononemia, epilepsy, brain malformation</td>
<td>Low plasma glutamine</td>
</tr>
</tbody>
</table>
Maple Syrup Urine Disease
Non-Ketotic Hyperglycinemia
Homocysteinemia

35 day F with suspected remethylation defect
Sulfite Oxidase Deficiency

Peroxisomal Disorders
Peroxisomes

- Peroxisomes are small intracellular organelles found in all nucleated cells

- Many functions facilitated by 50+ enzymes
  - Oxidation reactions
    - Beta-oxidation of very long chain fatty acids (VLCFA), PUFAs, and DCAs
    - Alpha-oxidation of branched chain fatty acids
    - Omega oxidation of fatty acids
    - Side chain of bile acid precursors (DHCA, THCA)
  - Synthesis of ether phospholipids (plasmalogens)
  - Synthesis of cholesterol (mevalonate kinase)
  - Detoxification of Glyoxylate
  - Other: lysine catabolism (pipecolic acid), glutaryl-CoA metabolism, H₂O₂ metabolism
Peroxisomal Disorders

• Biogenesis disorders
  – Abnormal importation of enzyme into the peroxisome
  – eg. Zellweger spectrum, rhizomelic chondrodysplasia punctata

• Single enzyme disorders
  – eg. Refsum disease, x-linked adrenoleukodystrophy

• All autosomal recessive
Zellweger Syndrome

- Clinical features
  - Craniofacial dysmorphism
  - Cataracts/corneal clouding
  - Retinopathy
  - Sensorineural hearing loss
  - Severe hypotonia
  - Seizures
  - Hepatopathy
  - Renal cysts
  - Chondrodysplasia punctata

- Average life expectancy 1-2 years
Zellweger Syndrome: Imaging

- Cortical malformations
  - perisylvian polymicrogyria, fronto-parietal pachygyria, heterotopias, germinolytic cysts
- Delayed myelination
- Later in childhood, demyelination including cerebellum and corticospinal tracts

Laboratory Evaluation for Zellweger syndrome

• Increased
  – plasma very long chain fatty acids
  – plasma pipecolic acid
  – plasma phytanic/pristanic acid (diet dependant, normal in neonate)
  – Urine and blood bile acid intermediates

• Decreased
  – RBC plasmalogenes
  – cholesterol
  – fat soluble vitamins
Lysosomal Disorders
Lysosomal Disorders

• Most are disorders of intra-lysosomal hydrolytic enzymes, some are transport disorders

• Most are autosomal recessive, except X-linked Fabry Disease and Danon Disease

• Presentation
  – “Hurler-phenotype”
  – Leukodystrophy
  – Neuronal degenerative disorders
    • Progressive myoclonus epilepsy (PME)
    • Non-PME
  – Other: Fabry disease, cystinosis, Pompe (GSD II), Danon disease, wolman disease
Hurler Phenotype

• Consists of
  – Coarse facies
  – Dysostosis multiplex (bony deformities) with short stature
  – Hernias (umbilical/inguinal)
  – Hepatosplenomegaly
  – Corneal opacities
  – Deafness
  – Cardiac: valvular defects, coronary artery occlusion

• Complications
  – Peripheral neuropathy, spinal stenosis, communicating hydrocephalus from storage
# Lysosomal Disorders: presentation

<table>
<thead>
<tr>
<th>Leukodystrophy</th>
<th>Hurler phenotype</th>
<th>PME</th>
<th>Neuronal degenerative disease (Non-PME)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krabbe Disease</td>
<td>Mucopolysacharidoses</td>
<td>Neuronal ceroid lipofuscinoses</td>
<td>Gaucher 2 &amp; 3</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Mucolipidosis 2 &amp; 3</td>
<td>Gaucher 3</td>
<td>Neimann Pick A &amp; C</td>
</tr>
<tr>
<td>Austin’s disease</td>
<td>Oligosaccharidoses</td>
<td>Sialidosis type 1</td>
<td>GM1 gangliosidosis</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>GM1 gangliosidosis</td>
<td>Sialidosis type 2</td>
<td>GM2 gangliosidosis</td>
</tr>
<tr>
<td>Salla Disease</td>
<td>Sialidosis Type 2</td>
<td>Galactosialidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galactosialidosis</td>
<td>GM2 gangliosidosis (rarely)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Austin’s disease</td>
<td>Sandhoff (rarely)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salla disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lysosomal Disorders: Additional Clinical Cues

- Cherry red retinal spot
- T2 dark thalami on MR
- Vacuolated lymphocytes
- Infantile hydrops
- Hepatosplenomegaly
- Supranuclear gaze palsy
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Laboratory Evaluation</th>
</tr>
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<tbody>
<tr>
<td>Mucopolysaccharidoses</td>
<td>Enzymology, urine glycosaminoglycans</td>
</tr>
<tr>
<td>Oligosaccharidoses</td>
<td>Enzymology, urine oligosaccharides</td>
</tr>
<tr>
<td>Mucolipidosis 2 &amp; 3</td>
<td>Enzymology (multiple increased enzymes)</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy, Austin disease, Saposin B deficiency</td>
<td>Arylsulfatase A activity, urine sulfatides (required to dx Saposin B deficiency)</td>
</tr>
<tr>
<td>Krabbe disease</td>
<td>Galactocerebrosidase activity</td>
</tr>
<tr>
<td>Gaucher</td>
<td>Glucocerebrosidase activity</td>
</tr>
<tr>
<td>Neimann-Pick type A</td>
<td>Sphingomyelinase activity</td>
</tr>
<tr>
<td>Neimann-Pick type C</td>
<td>Plasma oxysterols, skin bx for filipin staining and cholesterol esterification studies</td>
</tr>
<tr>
<td>Fabry disease</td>
<td>Alpha-galactosidase activity in males, (genetic studies required in females)</td>
</tr>
<tr>
<td>Pompe disease</td>
<td>Alpha-glucosidase activity</td>
</tr>
<tr>
<td>Danon disease</td>
<td>Genetic testing, muscle biopsy</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
<td>Genetic testing, skin/conjunctival biopsy for inclusions, enzymology in several</td>
</tr>
<tr>
<td>Free sialic acid storage disease/salla</td>
<td>Urine free sialic acid</td>
</tr>
</tbody>
</table>
Lysosomal Disorders: Treatment

• **Enzyme replacement therapy**
  – Fabry, Pompe, MPS I/II/VI, type I Gaucher

• **Bone marrow transplant**
  – Krabbe, metachromatic, MPS1

• **Substrate reduction therapy**
  – Neumann-Pick type C, Gaucher disease

• **Cyclodextrin**
  – Neumann-Pick type C
Disorders of Biogenic Amine (Neurotransmitter) Metabolism
Biogenic Amine Metabolism

Biogenic Amine Disorders

• Genetic defects in biosynthesis, transport, receptor binding, and degradation

• All autosomal recessive, except dominant GTP cyclohyrolase deficiency

• Presentation
  – Extrapyramidal symptoms
    • Dystonia, chorea, parkinsonism
    • May have diurnal variation
  – Dysautonomia
  – Oculogyric crises
  – Other: bipyramidal signs, hypotonia, developmental delay, epilepsy
  – Imaging normal (except in DHPR deficiency)
Biogenic Amine Disorders

• Lab
  – Disorders of biopterin metabolism
    • Plasma phenylalanine elevated in most
    • Urine pterins
    • RBC DHPR enzyme activity
  – Serum prolactin may be elevated in dopamine deficient state
  – CSF analysis
    • HVA, HIAA, 3-O-methyldopa
    • Biopterin profile
## Biogenic Amine Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Levels in Cerebrospinal Fluid</th>
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<tr>
<td></td>
<td>Neopterin</td>
</tr>
<tr>
<td>Dopamine beta-hydroxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>n</td>
</tr>
<tr>
<td>Aromatic-L-amino acid decarboxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>Monoamine oxidase A deficiency</td>
<td></td>
</tr>
<tr>
<td>Dopamine transporter deficiency</td>
<td>↑</td>
</tr>
<tr>
<td>Dopamine-serotonin vesicular transport defect</td>
<td>n</td>
</tr>
<tr>
<td>Guanosine triphosphate cyclohydrolase deficiency</td>
<td>↓</td>
</tr>
<tr>
<td>(autosomal recessive)</td>
<td></td>
</tr>
<tr>
<td>6-Pyruvoyl-tetrahydropterin synthase deficiency</td>
<td>↑↑</td>
</tr>
<tr>
<td>Dihydropteridine reductase deficiency</td>
<td>n</td>
</tr>
<tr>
<td>Pterin-4-α-carbinolamine dehydratase deficiency</td>
<td>↑-↑↑</td>
</tr>
<tr>
<td>(Primapterinuria)</td>
<td></td>
</tr>
<tr>
<td>Dopa-responsive dystonia (Segawa disease)</td>
<td>↓</td>
</tr>
<tr>
<td>Sepiapterin reductase deficiency</td>
<td>n</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- 5-HIAA = 5-hydroxyindoleacetic acid (derived from serotonin)
- 5-HTP = 5-hydroxytryptophan
- HVA = Homovanillic acid (derived from dopamine)
- 3-OMD = 3-ortho-methylidopa (derived from L-DOPA)
- MHPG = 3-methoxy-4-hydroxyphenylglycol (norepinephrine metabolite)


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# Biogenic Amine Disorders: Treatment

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Management</th>
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<tr>
<td>AD GTP cyclohydrolase deficiency</td>
<td>L-dopa</td>
</tr>
<tr>
<td>Additional biopterin disorders</td>
<td>BH4, L-dopa, and 5-hydroxytryptophan</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>L-dopa or dopamine agonists</td>
</tr>
<tr>
<td>L-aromatic amino acid decarboxylase deficiency</td>
<td>Pyridoxine/pyridoxal-phosphate, dopamine receptor agonist</td>
</tr>
<tr>
<td>Dopamine beta hydroxylase deficiency</td>
<td>Droxidopa</td>
</tr>
</tbody>
</table>
Newborn Screen

• Blood spot on filter paper card collected between 24-72 hours of age

• New England NBS program includes the following metabolic studies
  – Acylcarnitine analysis
  – Limited amino acid analysis (eg. no glycine, homocysteine)
  – Biotinidase enzyme activity
  – Qualitative succinylacetone (tyrosinemia type 1)
  – GALT enzyme assay and total galactose (galactosemia)

• False negatives (and positives) are possible, so if clinical concern then send diagnostic studies
<table>
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<tr>
<th>Category</th>
<th>Presentation</th>
<th>Diagnosis</th>
</tr>
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<tr>
<td>Urea cycle disorders</td>
<td>Hyperammonemic encephalopathy</td>
<td>Ammonia, plasma amino acids, urine organic acids</td>
</tr>
<tr>
<td>Fatty acid oxidation &amp; carnitine disorders</td>
<td>Hypoketotic hypoglycemia, episodic rhabdomyolysis, cardiomyopathy, hepatopathy</td>
<td>Plasma acylcarnitines, free/total carnitine</td>
</tr>
<tr>
<td>Organic acidemias</td>
<td>Ketoacidosis, hyperammonemia, metabolic stroke, developmental delay</td>
<td>Urine organic acids, plasma acylcarnitines</td>
</tr>
<tr>
<td>Aminoacidopathies</td>
<td>Epilepsy, developmental delay, acute CNS events (toxic, ischemic)</td>
<td>Plasma amino acids, additional metabolic studies based on suspected diagnosis</td>
</tr>
<tr>
<td>Peroxisomal disorders</td>
<td>Retinopathy, sensorineural hearing loss, brain malformation, dysmorphisms, leukoencephalopathy</td>
<td>Plasma VLCFAs, phytanic acid, pipecolic acid</td>
</tr>
<tr>
<td>Lysosomal disorders</td>
<td>Hurler phenotype, leukoencephalopathy, PME, cherry red spot, organomegaly, gaze palsy</td>
<td>Enzymology, urine MPS screen, urine oligosaccharides</td>
</tr>
<tr>
<td>Biogenic amine disorders</td>
<td>Movement disorder, diurnal fluctuation, dysautonomia, oculogyric crisis</td>
<td>CSF neurotransmitters, CSF/urine pterins, plasma phenylalanine</td>
</tr>
</tbody>
</table>
“Small Molecule Screen”

- Basic chemistry and blood gas
- Urine ketones
- Ammonia (free flowing, no tourniquet, on ice)
- Lactate (free flowing, no tourniquet, on ice)
  - add pyruvate if elevated for lactate/pyruvate ratio
- Plasma amino acids
- Total homocysteine
- Urine organic acids
- Plasma acylcarnitine profile
- Free/total carnitine
- +/- urine amino acids
Questions?
Useful Resources

• GeneReviews (http://www.ncbi.nlm.nih.gov/books/NBK1116/)

• Online Metabolic and Molecular Basis of Inherited Disease (OMMBID)

• Fernandes et al. Inborn Metabolic disease 4th edition

• Zschocke et al. Vademecum Metabolicum: Diagnosis and Treatment of Inborn Errors of Metabolism, 3rd edition

• New England Consortium of Metabolic Programs: Acute Illness Protocols (http://newenglandconsortium.org/for-professionals/acute-illness-protocols/)