A Generalist’s Approach to Inborn Errors of Metabolism

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Alberta Children’s Hospital
Objectives (Junior Residents)

By the end of this session, residents will be able to:

1. Categorize the various Inborn Errors of Metabolism
2. Describe several ways in which Inborn Errors of Metabolism can present
3. Name some initial screening labs when an Inborn Error of Metabolism is suspected
Objectives (Senior Residents)

By the end of this session, residents will be able to:

1. Categorize the various Inborn Errors of Metabolism
2. Describe the acute, and chronic ways that Inborn Errors of Metabolism can present
3. Know when to clinically suspect an Inborn Error of Metabolism
4. Order appropriate investigations, and interpret them to make a diagnosis of an Inborn Error of Metabolism
5. Begin management for a patient with a newly diagnosed metabolic disorder, and patient with a known metabolic disorder with acute deterioration
What is an Inborn Error of Metabolism?

A large group of rare genetic diseases that generally result from a defect in an enzyme or transport protein which results in a block in a metabolic pathway.

Remember…pattern recognition is key
Metabolic Principles

Clinical features and phenotypic spectrum of IEMs are widely variable

- Genetic variation
- Age
- Acuity
- Severity
- Systems affected

However, you can find common patterns in presentation by understanding biochemistry.
Clinical features of IEMs can result from direct and indirect effects of:

- Accumulated substrates proximal to the block (eg. Galactosemia)
- Effects on secondary pathways (eg. Hyperammonemia in OAs)
- Deficient products distal to the block (eg. Hypoglycemia in GSD type1a)
- Accumulation of unusual intermediates (eg. Secondary carnitine deficiency)
Disorders of protein metabolism
Protein Intake → Catabolism → Amino Acids → Deamination → Ammonia → Urea Cycle (Liver) → Organic Acid → Enzyme → Urea
PROTEIN METABOLISM: SIMPLIFIED

- Intake
  - Protein
    - Amino Acids
      - Deamination

AMINOACIDOPATHY

- Organic Acid
- Ammonia
- UreaCycle
- Liver

Enzyme
Protein Intake

Catabolism

Protein

Amino Acids

Enzyme

Deamination

Ammonia

Organic Acid

Organoic Acidaemia

Urea

Urea Cycle

Liver
PROTEIN METABOLISM: SIMPLIFIED

Intake → Protein → Catabolism → Amino Acids

Deamination

Organic Acid

Ammonia

UREA CYCLE DEFECT

Urea

Liver
Urea Cycle Defects
Protein Intake → Catabolism → Amino Acids → Deamination → Organic Acid → Enzyme → Urea Cycle → Liver → Urea Cycle Defect → Ammonia → Urea
Urea Cycle defects

- Clinical Presentation?
- Physical Exam?
- Labs?
Urea Cycle defects

- Clinical presentation
  - Generally presents first days of life
  - Altered LOC, lethargy, vomiting, cerebral edema
  - Tachypnea
  - Shock-like picture
  - Can present later – recurrent under-recognized episodes leading to developmental delay, protein aversion
Urea Cycle Defects

- Labs
  - Hyperammonemia
  - Respiratory alkalosis
  - No, or little urea – out of keeping of clinical state
  - May have hypoglycemia
  - Labs suggestive of multiorgan failure
  - Prolonged metabolic stress leads to pancytopenia
# Urea Cycle Defects

<table>
<thead>
<tr>
<th>Problem</th>
<th>Labs</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymatic deficiency</td>
<td>Hyperammonemia, Respiratory alkalosis</td>
<td>Lethargy, Obtundation, Seizures, Tachypnea</td>
</tr>
<tr>
<td>Progressive worsened feeding</td>
<td>Metabolic acidosis (mild)</td>
<td>Tachypnea, Poor perfusion/shock</td>
</tr>
<tr>
<td>Hypermetabolic/catabolic state</td>
<td>Hypoglycemia</td>
<td>Lethargy, Obtundation</td>
</tr>
<tr>
<td>Shock</td>
<td>End organ labs abnormal</td>
<td>Poor perfusion, End organ damage</td>
</tr>
</tbody>
</table>
Urea Cycle Defects

- Diagnosis
  - Serum amino acids, organic acids
  - Urine organic acids (urine orotic acid)
  - Genetics
Urea Cycle Defects

MANAGEMENT PRINCIPLES:

1. ABCs
2. Stop protein/amino acid source
   - Stop protein intake
   - Stop catabolic process
   - Treatment of the precipitating factor
3. Eliminate toxic metabolites
4. Prevent and monitor for sequelae
Urea Cycle Defects

Stop protein/aa source and stop catabolism

- Halt any PO/GT intake until discussed with metabolics – they need specialized formula
- Aim for anabolism
  - IV fluids – high rate and high dextrose (D10). Maintain IV until PO is fully tolerated
  - High caloric supplementation in consultation with metabolics. (carbs and lipids)
  - Consider insulin
- Treat the precipitant – infection, injury, surgery, puberty, dietary change
Urea Cycle Defects

*Eliminate toxic metabolites*

- Dialysis: Indicated if severe hyperammonemia, coma, severe electrolyte disturbances
- Sodium benzoate, sodium phenylbutarate
- L-carnitine (PO or IV): restores free carnitine levels (where carnitine levels are often low anyways)
Urea Cycle Defects

*Prevent and monitor for sequelae*

- Cerebral edema: Neurological monitoring. Maintain osmolality
- Other organ involvement
Urea Cycle Defects

Chronic/Long term management

- Protein restriction
- Arginine or citrulline supplementation
- Sodium or glycerol phenylbutyrate
- Sick day management
- Liver transplant
Urea Cycle Defects

Specific Urea Cycle Defects

- Ornithine Transcarbamylase Deficiency (OTC)
- CPS
- NAGS
- Arginosuccinate synthetase/lyase
- Arginase
Intake ➔ Protein ➔ Amino Acids ➔ Enzyme ➔ Deamination ➔ Organic Acid ➔ Ammonia ➔ N-acetylglutamate synthetase (NAGS) ➔ Urea Cycle ➔ Urea

Liver

N-acetylglutamate synthetase (NAGS) is competitively inhibited by ammonia, affecting urea cycle enzymes.
Organic Acidemias

- Clinical Presentation?
- Physical Exam?
- Labs?
Organic Acidemias

- Clinical presentation
  - Infancy
  - Progressively worse feeding
  - Vomiting and lethargy
  - Tachypnea
  - Shock
  - Multiorgan failure
  - Stroke
  - Late onset cardiomyopathy and cardiac dysrhythmia
Organic Acidemias

- Labs and diagnosis
  - Hyperammonemia
  - Anion gap metabolic acidosis
  - Marked ketonuria
  - May have hypoglycemia
  - Labs suggestive of multiorgan failure (hepatitis, renal failure, pancreatitis)
  - Prolonged metabolic stress leads to pancytopenia
## Organic Acidemias

<table>
<thead>
<tr>
<th>Biochemical problem</th>
<th>Labs</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased organic acid production</td>
<td>Hyperammonemia (NAG synthase inhibition)</td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
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<td>Obtundation</td>
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<td>Tachypnea</td>
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<td>Seizures</td>
</tr>
<tr>
<td>AG Metabolic acidosis (ketone and organic acid production)</td>
<td>AG Metabolic acidosis (ketone and organic acid production)</td>
<td>Tachypnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor perfusion/shock</td>
</tr>
<tr>
<td>Increased glucose utilization/hypermetabolic state</td>
<td>Hypoglycemia</td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obtundation</td>
</tr>
<tr>
<td>Ketosis and ketogenesis</td>
<td>Ketosis and ketogenesis</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatty liver/hepatomegaly (mobilized FFA stores)</td>
</tr>
</tbody>
</table>
Organic Acidemias

- Diagnosis
  - Urine organic acids
  - Acyl carnitine and carnitine profile
Organic Acidemias

MANAGEMENT PRINCIPLES:

1. ABCs
2. Stop protein/amino acid source
   - Stop protein intake
   - Stop catabolic process
   - Treatment of the precipitating factor
3. Eliminate toxic metabolites
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Organic Acidemias

*Stop protein/aa source and stop catabolism*

- Halt any PO/GT intake until discussed with metabolics – they need specialized formula
- Aim for anabolism
  - IV fluids – high rate and high dextrose (D10). Maintain IV until PO is fully tolerated
  - High caloric supplementation in consultation with metabolics. (carbs and lipids)
  - Consider insulin
- Treat the precipitant – infection, injury, surgery, puberty, dietary change
Organic Acidemias

Eliminate toxic metabolites

- Dialysis: Indicated if intractable acidosis, severe hyperammonemia, coma, severe electrolyte disturbances
- L-carnitine (PO or IV): Conjugates and detoxifies organic acids, and restores free carnitine levels (where carnitine levels are often low anyways)
- Carglumic acid: NAG analogue
Organic Acidemias

*Prevent and monitor for sequelae*

- Acute pancreatitis: Check amylase and lipase, monitor clinically
- Strokes: Neurologic monitoring. Consider CT/MRI if neuro symptoms
- Cerebral edema: Neurological monitoring. Maintain osmolality
- Other organ involvement
Organic Acidemias

Chronic/Long term management

- Dietary restriction
- Vitamin supplementation
- Carnitine supplementation
- Sick day management
- Transplantation
Organic Acidemias

Specific Organic Acidemias

- Propionic Acidemia
- Methylmalonic Acidemia
- Glutaric Acidemia
Aminoacidopathy
AMINOACIDOPATHIES

Intake
Protein
Amino Acids

Catabolism

Deamination

AMINOACIDOPATHY

Organic Acid
Enzyme

Ammonia
Enzyme

Urea
Enzyme

Urea Cycle
Liver
Why is the clinical presentation so heterogeneous? Because of THIS

Reference: https://step1.medbullets.com/biochemistry/102091/amino-acid-catabolism
Aminoacidopathies

- Enzymatic block prevents metabolism of CERTAIN amino acids (not all)
- Clinical presentation depends on which block occurs, and what the toxic metabolites are. Presentation in this group is highly variable
- Examples:
  - Phenylalanine (PKU)
  - Branched chain amino acids (MSUD)
Aminoacidopathies

Phenylketonuria - Deficiency of Phenylalanine hydroxylase (occasionally, due to a BH4 metabolism defect)

- Clinical presentation
  - Microcephaly
  - GDD
  - Eczematous rash
  - Mood and cognitive disorders
  - Teratogenic – infants would be dysmorphic, microcephalic, IUGR, CHD

- Diagnosis
  - Newborn screen
  - Plasma amino acids, urine organic acids

- Treatment
  - Dietary restriction of phe, monitor blood phe levels
  - BH4 supplementation

Reference: https://www.semanticscholar.org/paper/Food-products-made-with-glycomacropeptide%2C-a-whey-a-Calcar-Ney/f57c2c3d09518bd03c144db43f1857bddd98823d6/figure/0
Aminoacidopathies

Maple Syrup Urine Disease - Deficiency in branched chain a-ketoacid dehydrogenase

- Clinical presentation
  - Acute decompensations (high leucine intake, or catabolic stress)
  - Headache, confusion, hallucinations, lethargy, vomiting
- Diagnosis
  - Plasma amino acids, urine organic acids
- Treatment
  - Acute
    - Stop leucine intake
    - Stop catabolic stress (High dextrose, IV fluids, lipids, NG feeds)
    - Monitor for cerebral edema
    - Dialysis
  - Chronic
    - Life long leucine restriction

Disorders of Carbohydrate metabolism
Glucose Regulation

Eat

↑Glucose

+ Glycogenolysis
+ Gluconeogenesis
+ Lipolysis
+ Ketogenesis
- Glucose Uptake

↑Insulin

+ Glucose uptake in periphery
+ Glycogen synthesis
- Lipolysis
- Gluconeogenesis

↓Glucose

↑Glucagon
↑Growth Hormone
↑Cortisol
↑Epinephrine
Glycogen Storage Diseases
Glycogen Storage Disease

- Inability to degrade stored glycogen
- Extremely heterogeneous clinical presentations
GSD 1

- Clinical Presentation?
- Physical Exam?
- Labs?
GSD 1

- Clinical Presentation
  - Young (~3 month, when they start to stretch out their feeds)
  - Progressively poor feeding
  - Lethargy, seizures
  - Growth failure

- Physical Exam
  - Course facies? Cherubic
  - General – Lethargic, pale
  - CVS/Resp – Normal
  - Abdo – May have hepatomegaly

- Labs
  - Ketotic hypoglycemia
  - Lactic acidosis
  - Hyperuricemia
  - Hypertriglyceridemia
  - Type 1b has neutropenia
Acute decompensation management principles

1. ABCs
2. Provide glucose
3. Treat inciting factor
4. Monitor for acute complications/sequelae
GSD 1

- Long term complications
  - Neutropenia and frequent infections
  - Hepatic adenomas
  - Renal insufficiency
  - IBD

- Long term treatment
  - Cornstarch
  - Continuous feeds
  - Sick day monitoring
GSD 2 - Pompe

- Glucose
  - Glucose 6 Phosphate
    - Pyruvate
      - Lactate
      - Uric Acid
      - Fatty Acids → Triglyceride
  - Galactose
  - Fructose

- Glycogen
  - Glycogen Synthesis
  - Glycogenolysis

- Kreb Cycle
  - Electron Transport Chain
GSD2:

- Pompe disease (glycogen storage disease II, Acid alpha glucosidase (GAA)/acid maltase deficiency)
- More accurately classified as a lysosomal storage disease

Reference: https://hubpages.com/education/Genetic-Disorders-Pompe
Pompe Disease

- Pathophysiology: Deficiency of enzymes in lysosomes, leads to accumulation of glycogen (skeletal, cardiac, smooth muscle)

- Clinical Presentation:
  - Classic infantile-onset:
    - Pompe disease often presents in the first two months of life
    - Hypotonia, generalized muscle weakness, cardiomegaly and hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, respiratory distress, and hearing loss.
    - Death in the first year of life from progressive left ventricular outflow obstruction
  - Juvenile onset
    - Less cardiomyopathy than above
  - Adult onset
    - Progressive myopathy
    - Can present as late as 60s
Pompe Disease

Management

- Supportive
  - Cardiac (CM, arrhythmias)
  - Resp (Respiratory insufficiency, frequent infections, sleep disordered breathing)
  - GI (Poor feeding, aspiration, poor growth)
  - Neuro (Poor tone, motor delays, hearing impairment)
  - MSK (Weakness, contractures)

- Definitive Treatment: enzyme replacement therapy (ERT) within 1st 6 months of life
Galactosemia
Galactosemia

Glucose 6 Phosphate

Glycogen → Glycogenolysis → Glucose 6 Phosphate

Glycogen Synthesis → Glucose 6 Phosphate

Gluconeogenesis → Glucose 6 Phosphate

Glycolysis → Glucose 6 Phosphate

Fructose → Uric Acid → Lactate → Fatty Acids → Triglyceride

Galactose → Galactose

Electron Transport Chain → Kreb Cycle
Lactose → Glucose + Galactose

Reference: https://www.medicalhomeportal.org/diagnoses-and-conditions/galactosemia
Clinical Presentation

Reference: https://www.mountsinai.org/health-library/diseases-conditions/galactosemia
Galactosemia

- CNS: Developmental delay/low IQ, speech problems (vocabulary and articulation), abnormal motor function, ataxia
- HEENT: Cataracts
- CVS:
- GI: Hepatitis, hyperbilirubinemia, liver failure, cirrhosis
- GU: Renal impairment
- MSK: Decreased bone mineral density
- Heme: Bleeding and coagulopathy (secondary to liver failure)
- Endo: Growth delay, primary amenorrhea, premature ovarian failure
- ID: Sepsis (*Escherichia coli, Klebsiella, Enterobacter, Staphylococcus, Beta-streptococcus, Streptococcus faecalis*)
Galactosemia

• The diagnosis of classic galactosemia
  • elevated erythrocyte galactose-1-phosphate concentration
  • reduced erythrocyte galactose-1-phosphate uridylyltransferase (GALT) enzyme activity
  • Genetics (GALT)
  • Newborn screen – GALT enzyme activity
Galactosemia - treatment

Acute decompensation management principles

1. ABCs
2. Provide glucose
3. Treat/eliminate inciting factor (galactose)
4. Monitor for acute complications/sequelae
   • Hypoglycemia
   • Hyperbilirubinemia
   • Liver failure
   • Sepsis
   • Hyperammonemia
Treatment

- Galactose-free diet
  - Soy-based formulas
  - Elemental formula

- Experimental: inhibitors of the GALK enzyme
Disorders of lipid metabolism
Lipid Metabolism

- **Triglyceride**
  - E
  - Glycerol backbone
  - Free Fatty Acids (Acyl carnitine)

- **Lipolysis**

- **Glycerol back bone**

- **Acetyl-CoA**
  - B oxidation
  - ketones

- **Carnitine**

- **Kreb Cycle**

- **Gluconeogenesis**
Fatty Acid Oxidation Defects

- Basic Science: Deficiency in SCAD, MCAD, LCAD, or carnitine

- Clinical presentation
  - Normal at birth, developmentally appropriate
  - Presents in infancy or early childhood during prolonged fast
  - Hypoketotic hypoglycemia – lethargy, seizure, coma
  - Can present with sudden death
  - LCFAOD can also have rhabdomyolysis, cardiomyopathy, liver dysfunction
Fatty Acid Oxidation Defects

- Labs:
  - Hypoketotic hypoglycemia during acute episode
  - Hepatitis

- Diagnosis
  - Plasma Acylcarnitine profile
  - Urine organic acids
  - Carnitine (free and total)
Fatty Acid Oxidation Defects

- **Acute Treatment:**
  - When sick, high dextrose
  - NO lipids
  - Avoid prolonged fasting

- **Long term treatment**
  - Dietary fat restriction – can use MCT oil in LCFAOD
  - Carnitine supplementation
Complex Molecule/Organelle Disorders
Complex Molecule/Organelle Disorders

In general, presentation is different from “small molecules”

- Present more insidiously, less acute deteriorations
- “Storage” issues – organomegaly, course facies
- Neurological/developmental issues and regression
- Bony deformities
- Sensory issues
Peroxisomal Disorders

- Involved in beta oxidation of VLCFAs
- Defects lead to accumulation of VLCFA
- Examples: Zellweger, adrenoleukodystrophy

Peroxisomal Disorders

Zellweger
- Absent peroxisomes
- Dysmorphic
- Hypotonia
- Hearing and vision defects
- Seizures
- Liver disease
- MRI shows leukodystrophy

- Work up: MRI head, VLCFAs

Adrenoleukodystrophy
- X linked
- Deficiency is VLCFA oxidation
- School aged onset
- Developmental regression
- New spasticity
- Adrenal failure

- Work up: MRI head, VLCFAs
The image is a flowchart outlining the classification of inborn errors of metabolism, organized into categories such as Proteins, Carbohydrates, Lipids, Urea Cycle Defects, Organic Acidemia, Uric Acid Metabolism, and Mitochondrial metabolism. Each category further divides into subcategories, detailing specific disorders and their corresponding metabolic pathways or defects.
Lysosomal Storage Disorders

- Lysosomes – an organelle that digests large molecules for recycling or degradation
- Lysosomal storage disorders are due to inability to break these down, and progressive accumulation in tissues
  1. Mucopolysaccharides
  2. Sphingolipids
  3. Oligosaccharides

Reference: https://www.genome.gov/genetics-glossary/Lysosome
Mucopolysaccharidoses

- Clinical features
  - Progressive symptoms, wide spectrum of severity
  - Normal at birth
  - Coarse facial features
  - Corneal clouding
  - Bony deformities, short stature
  - Developmental regression, or cognitively normal
  - Visceromegaly
  - Tendency for hernias
  - Xray – dysostosis multiplex

- Treatment
  - Enzyme Replacement Therapy
  - Stem cell transplant

Reference: https://en.wikipedia.org/wiki/Mucopolysaccharidosis
Mucopolysaccharidoses

- Work up
  - Urine glycosaminoglycan (GAG)
  - Urine oligosaccharides
  - Lymphocyte or fibroblast enzymatic activity
  - Genetic testing
### PROTEIN
- Aminoacidopathy
  - Phenylalanine (PKU)
  - Tyrosine (Tyrosinemia, Albinism)
  - Methionine (Homocysteinuria)
  - Cysteine (Sulfite oxidase deficiency)
  - Tryptophan (Hartnup)
  - Branched chain amino acids (MSUD)
  - Glycine (Hypermethioninemia)

### Carbohydrate
- Glycogen Storage disease
  - GSD I – Von Gierke
  - GSD II – Pompe
  - GSD IV – Debrancher enzyme deficiency
  - Fackoni Bickel
  - McArdle

### Lipids
- B oxidation defects
  - SCAD
  - MCAD
  - LCAD
  - VLCAD

### Urea Cycle Defects
- CPS
- NAGS
- OTC
- Arginosuccinate synthetase/lyase

### Organine Acidemia
- Methylmalonic aciduria
- Propionic acidemia
- Isovaleric aciduria
- Multiple carboxylase deficiencies
- Glutaric acidemia

### Protein Metabolism
- Aminoacidopathy
  - Phenylalanine (PKU)
  - Tyrosine (Tyrosinemia, Albinism)
  - Methionine (Homocysteinuria)
  - Cysteine (Sulfite oxidase deficiency)
  - Tryptophan (Hartnup)
  - Branched chain amino acids (MSUD)
  - Glycine (Hypermethioninemia)

### Lipids
- B oxidation defects
  - SCAD
  - MCAD
  - LCAD
  - VLCAD

### Organic Acidemia
- Methylmalonic aciduria
- Propionic acidemia
- Isovaleric aciduria
- Multiple carboxylase deficiencies
- Glutaric acidemia

### Fructose 1-6-phosphatase deficiency
- Phosphorylase kinase deficiency
- Glycogen synthetase deficiency
- Fackoni Bickel
- McArdle
- Lactate dehydrogenase deficiency

### Disorders of Carbohydrate Metabolism
- Fructose
- Fructosuria
- Hereditary Fructose Intolerance

### Disorders of Lipid Metabolism
- Carnitine Disorders
  - Primary carnitide deficiency
  - Carnitine palmitoyltransferase I (CPTI)
- Oxidative Phosphorylation
  - Glutaric aciduria II
- Multiple Acyl CA Dehydrogenase deficiency

### Disorders of Pentose Metabolism
- Pentosuria
- Transaldolase deficiency

### Defect of Single Peroxisomal Enzymes
- X linked Adrenoleukodystrophy
- Childhood cerebral form
- Adolsecent
- Adrenomyeloneuropathy

### Other
- Disorders of Metal Metabolism
- Purine and Pyrimidine Metabolism
- Other
Mitochondrial Disorders

- Responsible for energy production (Remember that Kreb cycle?)
- Defects in mitochondria affect tissues with the highest energy demand (brain, cardiac muscle, skeletal muscle)
- Inheritance:
  - If defect in mitochondrial genome – maternal
  - If defect in nuclear genes required for mitochondria to function, mendelian

Reference: https://www.genome.gov/genetics-glossary/Mitochondria
Mitochondrial Disorders

- Work up
  - Lactate may be elevated
  - MRI
  - Muscle biopsy (ragged red fibres)
  - Specialised DNA testing
  - Assays for respiratory chain activity
Resources


- Gregory M. Rice, Robert D. Steiner. Inborn Errors of Metabolism (Metabolic Disorders). *Pediatrics in Review*. January 2016, VOLUME 37 / ISSUE 1

- [https://newenglandconsortium.org/](https://newenglandconsortium.org/)

- Gene reviews
Questions

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