A Brief Historical Overview
Sir Archibald Garrod

THE INCIDENCE OF ALKAPTONURIA:
A STUDY IN CHEMICAL INDIVIDUALITY

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Sir Archibald Garrod

- Alkaptonuria followed autosomal inheritance
- hypothesized that it was caused by a mutation in a gene encoding an enzyme involved in the metabolism of ‘alkaptans’
- *The Incidence of Alkaptonuria: a Study in Chemical Individuality* in 1902
- formulated the "one gene, one enzyme" hypothesis and described recessive inheritance in enzyme defects
- presented this work to the Royal College of Physicians in a lecture entitled *Inborn Errors of Metabolism* in 1908.
Inborn Errors of Metabolism

• Genetic disorders involving disorders of metabolism.
• Most are enzyme defects disrupt conversion of substrates into products.
• In most of the disorders, problems arise due to accumulation of toxic upstream substances, or to the effects of reduced downstream essential compounds.
Inborn Errors of Metabolism

- Substrate
  - Upstream metabolites
- Enzyme
- Product
  - Downstream effects
One gene, One enzyme
Autosomal Recessive Inheritance

Father  

Mother

Children
Definition: Organic Acidemia

• Organic acidemias are characterized by abnormal amounts or types of organic acids in the urine and other body fluids.

• The diagnosis is made by detecting an abnormal pattern of organic acids in a urine sample—via GC/MS.

• In some conditions, the urine is always abnormal, in others the diagnostic organic acids are present (or at high levels) only intermittently.
Diagnosis and treatment overview
Examples of Organic Acidemias (OAs)

- Disorders of Branch Chain amino acid metabolism
- Cerebral organic acidemias
- Ketogenesis/Ketolysis disorders
- and other disorders
3 different clinical presentations

- Most characteristic of disorders of branch chain amino acid metabolism
- Severe, neonatal-onset form
- Acute, intermittent, late-onset form
- Chronic, progressive form
Severe, neonatal-onset form

- Symptoms begin after a brief symptom-free period (hours or weeks)
- Drowsiness progresses to poor feeding, lethargy, possibly coma
- Abnormal laboratory values
  - Acidosis
  - Elevated ammonia
  - Elevated lactate
  - Hyper or hypoglycemia
  - Pancytopenia
Acute, intermittent, late-onset form

- 25% of cases
- Present after symptom-free period
  - After 1 year of age
- Recurrent crises
- Onset of crises may be precipitated by catabolic stress
  - i.e. illness, high protein intake.
Chronic, progressive form

• Persistent poor feeding, chronic vomiting
• Low tone
• Failure to thrive
• Developmental delay
• May be misdiagnosed as milk-protein intolerance, celiac disease or other more common chronic illnesses
Diagnosis

• Newborn Screen
  – Results must be confirmed by definitive testing
• Detection of organic acids in the urine
  – Urine organic acids
  – Acylglycines
• Detection of organic acid metabolites in the blood
  – acylcarnitines
Organic Acid Analysis
Principles of Treatment

Substrate → Enzyme → Product

- Substrate
- Product
- Enzyme

Arrows indicate the flow from Substrate to Product through the enzyme.:

- Upstream substrates
- Alternative substrate metabolism
- Downstream effects
General Principles of Treatment

• Prevention of triggers for decompensation
  – Fever, illness, protein overload, dehydration

• Correct acute/sudden changes in body metabolism
  – Correct acidosis, hyperammonemia, glucose imbalance

• Reduce toxic substrates
  – Organic acids, etc.
OA of Branch Chain Amino Acid (BCAA) Metabolism: Methylmalonic Acidemia
First OA of BCAA reported: Propionic Acidemia

- First reported in 1961
  - Ketones, hyperglycinemia
  - Developmental delay
  - Neutropenia

- Primary biochemical abnormality described later
  - Propionic Acidemia
Methylmalonic Acidemia

- $1/50,000$
  - defect in MUT
  - vitamin B12 metabolism
- Massive elevation of MMA in all body fluids
- Acute Crises
  - episodic metabolic acidosis/decompensation
  - metabolic stroke
  - pancreatitis
- Chronic Medical Conditions
  - kidney failure,
  - failure to thrive,
  - intellectual disability
  - cardiomyopathy
  - optic nerve atrophy
Morbidity in MMA/PA/IVA

Methylmalonyl CoA → Succinyl CoA

**Upstream substrates**
- MMA
- PA

**Alt substrate metabolism**
- Methylcitrate
- Methymalonylcarnitine
- Propionylcarnitine
- propionylglycine

**Downstream effects**
- ? Defective TCA cycle
- ?mitochondrial dysfunction

**Targets for Treatment**
- MUT
Further downstream disturbance: Mitochondrial Dysfunction

Principles of Therapy: MMA

• Chronic management
  – Prevention of triggers for decompensation
    • Fever, illness, protein overload, dehydration
  – Dietary management
    • Protein, fat, carbohydrate balance

• Acute management
  – Correct acute/sudden changes in body metabolism
    • Acidosis, hyperammonemia, glucose

• Mitochondrial protection?
  – Antioxidants
Cerebral OA:
Glutaric Acidemia, Type I
Glutaric Acidemia Type I

- Deficient function of GCDH
- Inability to metabolize lysine, hydroxylysine, and tryptophan
- The products of alternative metabolism of this defect are neurotoxic
  - Glutaric Acid
  - Glutaryl-CoA
  - Glutaconic acid
  - 3-hydroxyglutarate
Cerebral Metabolic Crisis

• >90% of untreated patients will have an acute brain injury b/w 3-36 months
  • Typically bilateral striatal infarction

• Acute loss of physical abilities
  – Ability to sit, swallow, maintain head control
  – Profound hypotonia

• Leads to a permanent, often severe movement disorder
Lysine Metabolism

- Tryptophan
- Lysine
- Hydroxylysine

- Glutaryl CoA
- Crotonyl CoA
- Ketones

- Glutaric Acid
- Glutaryl Carnitine
- Glutaconic Acid
- 3-hydroxyglutarate

Enzyme: GCDH
Principles of Treatment

Lysine

Blood brain barrier

Lysine

Glutaric Acid
Glutaryl Carnitine
Glutaconic Acid
3-hydroxyglutarate
Managing Blood Brain Barrier Transport

Kevin A. Strauss, Joan Brumbaugh, Alana Duffy, Bridget Wardley, Donna Robinson, Christine Hendrickson, Silvi...
Treatment

- Employ a formula to restrict cerebral lysine uptake
  - competition between lysine and arginine at the blood–brain barrier
- Lys and Arg share a common cerebrovascular cationic transporter (y + system)
- Highly successful in preventing cerebral crises
Disorder of Ketogenesis:
HMG-CoA Lyase Deficiency
HMG CoA Lyase Deficiency

- Defective function of 3-Hydroxy-3-Methylglutaryl-CoA Lyase
  - crossover between ketogenesis and leucine metabolism
- Insufficient production of the ketones acetyl-CoA and acetoacetate
  - Leads to glucose overutilization
  - Hypoglycemia, lactic acidosis, liver dysfunction
HMG CoA Lyase Deficiency

Fatty Acids → HMG-CoA Lyase → AcetoAcetate

Leucine → HMG-CoA → 3-hydroxyisovaleric acid, 3-methylglutaconic Acid, 3-hydroxy-3-methylglutaric Acid

HMG-CoA Lyase Deficiency results in accumulation of 3-hydroxyisovaleric acid, 3-methylglutaconic Acid, and 3-hydroxy-3-methylglutaric Acid.
Treatment: Avoid Need for Ketones

- High carbohydrate, moderate protein and low fat diet
- Prevention of triggers for decompensation
  - Fever, illness, fasting, dehydration
- Correct acute/sudden changes in body metabolism
  - Correct acidosis, hypoglycemia
Summary

- OAs are a heterogeneous group of inherited genetic conditions that result in accumulation of metabolites with similar chemical structures ("organic acids")
- Treatment is centered around
  - Preservation of metabolic stability
  - Management of acute crises
- The upstream and downstream metabolic consequences are better understood and better controlled on some disorders more than others
- Advances in understanding many OAs is rapidly progressing
Thank you and Questions