Mohammed El-Khateeb

Inborn Error Of Metabolism

MGL-9
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Genetic diseases

- **Single gene disorders**
  - Caused by individual mutant gene
  - *Example: Inborn errors of metabolism*

- **Chromosomal disorders**
  - Numerical disorders
  - Structural disorders

- **Multifactorial disorders**
IEM are a large group of hereditary biochemical diseases in which specific gene mutation cause abnormal or missing proteins that lead to altered function.
Basic Principles

- Although individually rare, altogether they are 1:800-5000 incidence.
- **Broadly Defined:** Group of congenital disorders caused by an inherited defect in a single specific enzyme that results in a disruption or abnormality in a specific metabolic pathway.
- An inherent deficiency in a key metabolic pathway resulting in:
  - Cellular Intoxication
  - Energy deprivation
  - Mixture of the two
Central Dogma of Genetics

1. Replication
2. Reverse Transcription
3. Transcription
4. Translation
5. Protein
• Chemical Individuality
  Garrod 20\textsuperscript{th} Century
  Developed “Inborn Error of Metabolism”

• Beadle & Tatum
  Developed one gene one enzyme concept
An integrated view of the metabolic pathways

PROTEIN
- AMINO ACIDS
  - AMMONIA
    - UREA CYCLE
      - UREA
  - ORGANIC ACIDS
    - GLYCOGEN
      - GLUCOSE
        - PYRUVATE
          - ACETYL CoA
            - KREBS CYCLE
              - NADH
                - ATP
              - KETONES
        - LACTATE
      - FRUCTOSE
        - GALACTOSE
      - FREE FATTY ACIDS
  - LIPID
    - ORGANIC ACIDS

Theoretical consequences of an enzyme deficiency.

Defective enzyme

Substrate (increased) → Action → Product (decreased)

Co-factor A

Co-factor B

other enzymes

Metabolites (increased) → EFFECT ON OTHER METABOLIC ACTIVITY e.g., activation, inhibition, competition → Metabolites (decreased)
Inborn Errors of Metabolism

*a genetic disease*

*also known as biochemical genetics*

**Gene-level**

Gene mutation

**Protein-level**

Abnormal protein

- Enzyme
- Transpor protein
- Other protein

**Metabolic-level**

Abnormal metabolites
Inborn Errors Overview

- **General mechanism of problems**
  - Substrate accumulates to toxic levels
  - Toxic byproducts produced from shunting of accumulated substrate
  - Deficiency of end product
  - Poor regulation results in overproduction of intermediates to toxic level
BASIC IDEA,

Complex compound (Glycogen) ▶ Accumulate ▶ Organomegaly, Storage diseases

Intermediate substance (tyrosine) ▶ Accumulate ▶ Toxic

Simple molecules (propionic A) ▶ Accumulate ▶ Toxic

Energy (Glucose) ▶ Deficiency ▶ Energy defects
Inborn Errors of Metabolism

An inherited enzyme deficiency leading to the disruption of normal bodily metabolism

- Accumulation of a toxic substrate (compound acted upon by an enzyme in a chemical reaction)
- Impaired formation of a product normally produced by the deficient enzyme
GENETIC CHARACTERISTIC AND MODE OF INHERITANCE

- IEM are usually **Autosomal recessive**.
- Consanguinity is always relatively common.
- Some are **X-linked recessive** condition including:
  - Adrenoleukodystrophy.
  - Agammaglobulinemia.
  - Fabry’s disease.
  - Granulomatous disease.
  - Hunter’s Syndrome.
  - Lesch - Nyhan Syndrome.
  - Menke’s Syndrome.
- A few inherited as **Autosomal dominant trait** including: porphyria, hyperlipedemia, hereditary angioedema.
What is a metabolic disease?

• Small molecule disease
  – Carbohydrate
  – Protein
  – Lipid
  – Nucleic Acids

• Organelle disease
  – Lysosomes
  – Mitochondria
  – Peroxisomes
  – Cytoplasm
Categories of IEM

Disorders of:

• Amino acids
• Carbohydrates
• Fatty acid
• Lysosomal and peroxisomal function
• Mitochondrial
• Organic acids
DISORDERS OF AA METABOLISM

• PHENYLKETONURIA
• ALKAPTONURIA
• OCULOCUTANEOUS ALBINIS
• HOMOCYSTINURIA
• BRANCHED AMINOACIDS
PHENYLKETONURIA (PKU)

- **Clinical features:** Development delay in infancy, neurological manifestations such as seizures, hyperactivity, behavioral disturbances, hyperpigmentation and MR.

- **Incidence:** 1/5000 - 1/16000.

- **Genetics:** AR, 12q22-q24, > 70 mutations

- **Basic Defect:** Mutation in the gene of PA hydroxylase. PA-Tyrosine

- **Pathophysiology:** PA or derivatives cause damage in the developing brain

- **Treatment:** Dietary reduction of phenylalanine within 4W

- **Significance:** Inborn Metabolic disorder, The first Dietary restriction treatment. Mass screening of newborns
PHENYLKETONURIA

Tyrosinase

PA Hydroxylase D

Dietary Protein

Phenylalanine

Tyrosine

Phenylpyruvic acid

Melanin

Albinism

Tyrosinosis

2,5-dihydroxyphenylpyruvic acid

Homogentisic acid

Alkaptonuria

CO₂+H₂O
Two Types

- **PAH Deficient** (97% of cases)
  - Deficiency of PAH

- **Non-PAH Deficient** (3% of cases)
  - Defects in tetrahydrobiopterin or other components in related pathways
    - Dihydropterozin reductase deficiency
    - Dihydrobiopterin synthetase deficiency
Diagnostic Criteria

• Normal: 120 – 360 umol/L
• PAH Deficient:
  – Mild: 600 – 1200 umol/L
  – Classical: > 1200 umol/L
• Non-PAH Deficient:
  – < 600 umol/L
• Guthrie Bacterial Inhibition Assay
• Confirmation of diagnosis
PKU Mutations
Number of detected PKU

Year   Guthrie test available
1994   10
1998   36
2002   62
2005   116

46.5 %
Detected after availability of Guthrie Test
ALKAPTONURIA

- Autosomal Recessive described by Garrod
- Due to Homogenstic acid accumulation
- Excreted in Urine. Dark color in exposure to the air
- Dark pigment deposited in ear wax, cartilage and joints
- Deposition in joints known as Ochronosis in later life can lead to Arthritis
Alkaptonuria - Biochemistry

- **Alkaptonuria** reflects the absence of **homogentisic acid oxidase** activity.

![Biochemistry diagram](image-url)

**Alkaptonuria**
Symptoms of alkaptonuria

Normal urine

Urine from patients with alkaptonuria

Patients may display painless bluish darkening of the outer ears, nose and whites of the eyes. Longer term arthritis often occurs.
OCULOCUTANEOUS ALBINISM

- OCA is AR due to tyrosinase deficiency no melanine formation
- No pigment in skin, hair, iris and ocular fundus
- Nystagmus
- Genetically and biochemically heterogeneous
  - Classical tyrosinase negative
  - Tyrosinase positive, reduced enzyme level (type 1) OCA 1 located on chromosome 11q.
  - OCA 2 on chromosome 15q (pink-eye)
  - Third loci OCA-3 not related to above mentioned
HOMOCYSTINURIA

Sulfur AA metabolism disorders due to Cystathionin β-synthetase

- **Clinically:** MR, fits, Thromboembolic episodes, Osteoporosis, tendency to lens dislocation, scoliosis, long fingers and toes
- **Diagnosis:** positive cyanide nitroprusside in urine confirmed by elevated plasma homocystine
- **Treatment:** diet with low methionine and cystine supplement
- Some are responsive to pyridoxine as a cofactor to the deficient enzyme
Branched Chain Amino Acids

- 40% of preformed AA used by mammals are BCAA Valine, Leucine, Isoleucin
- Energy supply through $\alpha$-ketoacid decarboylase enzyme
- BCAA disease composed of 3 catalytic and 2 regulatory enzyme and encoded by 6 loci
- Deficiency in any one of these enzymes cause MSUD
- Untreated patients, accumulation of BCAAs cause neurodegeneration leads to death in the first few months of life
- Treatment BCAAs restriction diet
- Early detection
- Gene therapy ?????
MAPLE SYRUP URINE DISEASE

AR, due to deficiency in the branched chain ketoacid decarboxylase

• **Clinical:** Vomiting in the first week of life leading to death within few weeks

• **Diagnosis:**
  - Characteristic odor of urine
  - Presence of branched valine, leucine and isoleucine in urine and plasma

• **Treatment:** Diet deficient of the three AA
People with MSUD Have a Defective BCKD Protein Complex

Leusine           Isoleucine         Valine

Alpha-Ketoacid dehydrogenase complex

Isovaleryl-CoA    methylacetoacetyl CoA

propionyl CoA

methymalonyl CoA

succinyl CoA CoA
Urea Cycle Defects:

- UC main function to prevent accumulation of N₂ waste as urea
- UC main function to prevent accumulation of N₂ waste as urea
- Symptom free period and then emesis→lethargy--→COMA
- Key features:
  - High Ammonia, low BUN
  - Possible Lactic acidosis
  - *Absence of ketonuria*
  - NI to mild low Glucose
- Treat high ammonia, infuse glucose, send plasma AAs/OAs, urine orotic acid, and plasma citrulline.
- Infusion of 6ml/kg 10% Arginine HCl over 90 min may help.
- Milder forms may show episodic emesis, confusion, ataxia, and combativeness after **high protein meals**.
DISORDERS OF CH METABOLISM

MONOSACCHARIDE

1. **GALACTOSEMIA:** Deficiency of galactose-1-phosphate uridylyltransferase enzyme needed for the metabolism of both glucose and galactose.
   
   • **Clinical:** new bone, vomiting, lethargy, failure to thrive and jaundice
   
   • **Diagnosis:** reducing substances in urine, Gothri

2. **HEREDITARY FRUCTOSE INTOLERANCE:** Fructose 1-phosphate aldolase deficiency
   
   • **Diagnosis:** Fructose in Urine + Enzyme in the intestine mucosa and liver bx
   
   • **Clinical:** Mild to severe
   
   • **Treatment:** Diet restriction
Galactosemia:

- First 1-2 wks of Life: Presents with hypoglycemia, jaundice, emesis.
- Secondary to intolerance of Galactose. Will be in baby’s first meals of breast milk or lactose containing formulas.
- Also index of suspicion for GramNeg or E.coli sepsis.
- Dx assisted by Non-glucose reducing substances in urine.
- Confirmation by Galactose-1-PO uridyl transferase activity in RBCs.
- Adverse sequelae include Cataracts, MR, persistent liver disease.
Galactosemia

Galactose → enzyme action → galactose-1-phosphate → enzyme action → glucose-1-phosphate → enzyme action → glucose-6-phosphate

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Galactocemia: How does it happen?

- Dietary Lactose
- Galactos
- Galactose 1-Phosphate
- Glucose
  - BRAIN: Mental retardation
  - LIVER: Jaundice, Hetaptomegaly, Cirrhosis
  - EYES: Cataracts
Glycogen storage diseases (GSD)

Uridine-Diphosphogluucose

1. Glycogen synthetase

Glycogen Straight chains

2. Brancher enzyme (GSD-IV)

Glycogen Branched structure

3. Debrancher enzyme (GSD-III)

Limit dextrin + Glucose-1-PO4

4. Glucose-6-phosphatase (GSD-1)

Glycogen (normal branch) + Glucose

Glucose-1-PO4
# Glycogen Storage Disorders

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DEFECT</th>
<th>MAJOR AFFECTED TISSUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (Von Gieke)</td>
<td>Glucose – 6 – Phosphatase</td>
<td>Liver, Kidney, Intestine</td>
</tr>
<tr>
<td>Ib</td>
<td>Microsomal G6P transport</td>
<td>Liver, Kidney, Intestine, Neuroto</td>
</tr>
<tr>
<td>Ic</td>
<td>Microsomal phosphate transport</td>
<td>Liver, Kidney, Intestine</td>
</tr>
<tr>
<td>Id</td>
<td>Microsomal Glucose transport</td>
<td>Liver</td>
</tr>
<tr>
<td>II (Pompe)</td>
<td>Lysosomal acid a-glucosidase</td>
<td>Muscle</td>
</tr>
<tr>
<td>IIIa (Cori)</td>
<td>Glycogen Debranching enzyme</td>
<td>Liver, Muscle</td>
</tr>
<tr>
<td>IIIb</td>
<td>Glycogen Debranching enzyme</td>
<td>Liver</td>
</tr>
<tr>
<td>IV (Anderson)</td>
<td>Branching Enzyme</td>
<td>Liver, Muscle</td>
</tr>
<tr>
<td>V (McArdle)</td>
<td>Muscle phosphorylase</td>
<td>Muscle</td>
</tr>
<tr>
<td>VI (Hers)</td>
<td>Liver Phosphorylase</td>
<td>Liver</td>
</tr>
<tr>
<td>VII (Traui)</td>
<td>Muscle Phosphofructokinase</td>
<td>Muscle</td>
</tr>
</tbody>
</table>
Glycogen storage diseases (GSD)

Types:
• Hepatic/muscle involvement (GSD-III)
• Isolated Hepatic involvement (GSD-I, IV & VIII)
• Isolated muscle involvement (GSD-V & VII)
• Multiple tissues (GSD-II & IV)
GSD-II (Pompe disease)

- 6-month
- Hypotonia, Cardiomegaly & Hepatosplenomegaly
- Normal Glucose
- Do to an accumulation of glycogen in lysosomes.
- Manifested by massive Cardiomegaly, Hepatomegaly, Macroglossia.
- Fatal If results in CHF.
- Limited therapies in Neonatal Variant

**Acid α-glucosidase**

Glycogen $\rightarrow$ D-glucose 1-phosphate
Glycogen Storage Disorders:

- **Type 1 = Von Gierke’s:**
  - Shortly after birth: Severe lifethreatening Hypoglycemia
  - Lactic acidosis –due to isolated glycolysis of G6P
  - Hyper-uricemia, hyper lipidemia
  - Increased association with epistaxis
  - Hepatomegaly
  - Adverse response to Glucagon with worsening Lactic acidosis
Glycogen Storage Disorders:

- **Type 1 = Von Gierke’s:**
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  - *Hepatomegaly
  - **Adverse response to Glucagon with worsening Lactic acidosis
Lipid Metabolism

- Backbone of phospholipids and sphingolipids = biological membranes and hormones
- Intracellular messengers and energy substrate
- Hyperlipidemia, due to defective in lipid transport
- Fatty Acidemias is less common (fatty acid oxidation)
- FA mobilization from adipose tissue to cell = energy substrate in liver, skeletal and cardiac muscles
- FA transport across outer and inner mitochondrial membrane and entry into mitochondrial matrix
- Defects in any of these steps cause disease (Short, Medium & Long chain fatty acidemias)
Fatty Acid Oxidation Defects:

- Autosomal recessive inheritance
- Examples are LCAD, MCAD, LCAD
- Defect in acyl-CoA Dehydrogenase, a mitochondrial duty, and important in fasting state.
- KEY features:
  - Acute attack of life-threatening coma with Hypoglycemia
  - Absence of urine ketones, and reducing substances, serum AAs.
  - +/- mild acidosis, or hyperammonemia, elevated LFTs, abnl coags. +/-Hepatomegaly-/+ 
  - Dx with serum Acylcarnitine Profile or fibroblast enzyme assay
- GENETICS:
  - Missence mutation A → G results in substitution of glucose for lysine
  - Insertion
  - Deletion
- DIAGNOSIS: DNA newborn
LDL Receptor Pathway and Regulation of Cholesterol Metabolism
Mucopolysaccharides (glycosaminoglycans)
- Bone, connective tissue, skin, cornea, joints etc

Cell membranes, organelles
- Sphingolipids, glycolipids etc

Bacteria, viruses
- Glycogen

Food particles
- Lysosome
  - “The cells wrecking crew”

Abnormal lysosomal storage leads to developmental regression
LYSOSOMAL STORAGE DISEASE

- The hydrolytic enzymes within lysosomes are involved in the breakdown of sphingolipids, glycoproteins, and mucopolysaccharides into products.

- These molecular complexes can derive from the turnover of intracellular organelles or enter the cell by phagocytosis,

- A number of genetic diseases lacking lysosomal enzymes result in the progressive accumulation within the cell of partially degraded insoluble products, This condition leads to clinical conditions known as: lysosomal storage disorders.
Lysosomal Storage Disorders

- Resulted from accumulation of substrate
- Deficiency or inability to activate or to transport the Enzymes within lysosomes that catalyses stepwise the degradation of:
  - Glycosaminoglycans (MPS)
  - Sphingolipids
  - Glycoproteins
  - Glycolipids
- May be it is a result of genetic drift and natural selection
- Children normal at birth, downhill course of differing duration
Sphingolipidoses

• **Tay-Sachs disease**  
  AR  
  Hexosaminidase -A  
  – Developmental regression, Blindness,  
  – Cherry-red spot, Deafness

• **Gaucher's disease**  
  AR  
  Glucosylcerarnide Type I  
  β- Glucosidase Type II  
  – Joint and limb pains, Splenomegaly  
  – Spasticity, fits; death

• **Niemann-Pick disease**  
  AR  
  Sphingomyelinase  
  – Failure to thrive, Hepatomegaly  
  – Cherry-red spot, Developmental
Tay-Sachs Disease  
lysosomal storage disease

**Normal**

- $G_M^2$ ganglioside
  - sphingolipid
- hexosaminidase
- degradation products
- removal/recycling of sphingolipid components

**Tay-Sachs Disease**

- $G_M^2$ ganglioside
- hexosaminidase
- $G_M^2$ ganglioside accumulates in the lysosomes

Neurodegeneration
The cherry-red spot of Tay Sachs

Circle surrounds the macula. The “cherry red” center is the normal retina surrounded by white due to abnormal storage of $G_{M2}$ in retinal neurons.
### Common mutations associated with Tay-Sachs disease

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>4bp ins. (ex. 11)</td>
<td>Premature stop codon</td>
<td>~80%</td>
<td>~32%</td>
</tr>
<tr>
<td>G to C at spl. jct.</td>
<td>def. splicing</td>
<td>~10-15%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>G269S</td>
<td>&lt;3% act.</td>
<td>~2-3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>other</td>
<td>variable</td>
<td>&lt;1%</td>
<td>&gt;80%</td>
</tr>
</tbody>
</table>
Tay-Sachs disease: \((AR)\)
Rare in some populations and common in others.

Frequency of Tay-Sachs is about:
- 1/360,000 live births for non-Ashkenazi North Americans, and
- 1/3600 for North American Ashkenazi Jews

Carrier frequencies are therefore about:
- 1/300 for most North Americans, and
- 1/30 for North American Ashkenazi Jews

Disease and carrier frequencies in some other ethnic groups (French Canadians, Louisiana Cajuns, and Pennsylvania Amish) are comparable to those seen among Ashkenazi Jews.
Peroxisomal Disorders

- **Zellweger Syndrome**
- aka: **Cerebro-hepato-renal syndrome**
- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- When screening for PDs. obtain **serum Very Long Chain Fatty Acids-VLCFAs**
Leukodystrophies:

- **Krabbe disease:**
  - **Type 1-** “Infantile” = irritability, hypertonia, hyperesthesia, and psychomotor arrest, followed by rapid deterioration, optic atrophy, and early death
  - **Type 2-** Late infantile
  - **Type 3-** Juvenile
  - **Type 4-** Adult

- A demyelination disorder due to CNS accumulation of galactosylceramide.

- **Diagnosis:** supported by cortical atrophy on CT/MRI, **High CSF protein** and definite evidence of deficient
<table>
<thead>
<tr>
<th>Disease</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1 Gangliosidosis.</td>
<td>β - galactosidase</td>
</tr>
<tr>
<td>GM2 Tay -Sach.</td>
<td>Hexosaminidase A</td>
</tr>
<tr>
<td>Sandhoff disease.</td>
<td>Hexosaminidase A+B</td>
</tr>
<tr>
<td>Niemann – Pick disease.</td>
<td>Sphingomylinase</td>
</tr>
<tr>
<td>Gaucher’s disease.</td>
<td>Acidic - β - Glucosidase</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy.</td>
<td>Arylsulfatase A Neuronal ceroid lipofuscinosis</td>
</tr>
</tbody>
</table>
Mucopolysaccharidosis (MPS)

- **Types**: Seven types
- **Symptoms & signs**
  - Developmental delay.
  - Behavioral dysfunction
  - Coarse facial features & other somatic features
  - Cloudy cornea
  - Abdominal distension (Hepatosplenomegaly)
  - Dysostosis multiplex (Scoliosis and gibbous deformity)
- **Diagnosis**
  - Urine for MPS (heparan, keratan, dermatan)
  - Enzyme assay
Infant with coarse facies, severe DD, hypotonia, respiratory insufficiency & infections restrictive joint mobility & Hepatosplenomegaly

GM-1 Ganglioside → Acid β-galactosidase → GM-2 Ganglioside

Accumulate in brain & viscera
Mucopolysaccharidosis

- Heterogenous caused by reduced degradation of one or more of glycosaminoglycans
  - Dermatan sulfate  heparin sulfate
  - Keratan sulfate  Chondritin sulfate
- MPS are the degradation products of proteoglycans found in the extracellular matrix
- 10 different enzyme deficiencies cause 6

**Diagnosis**
- Clinical, Biochemical and Molecular analysis,
- Measurement of the enzyme in fibroblast, leukocytes, serum
- Prenatal diagnosis on Amniocytes or

**Genetics**: All AR except Hunter syndrome X linked

**Clinical**: Progressive multisystem deterioration causing:
  - Hearing, Vision, Joint and Cardiovascular dysfunction
Purine/pyrimidine metabolism

- **Lesch-Nyhan disease** (XR)
  - Hypoxanthine Guanine Phosphoribosyltransferase Deficiency
  - Mental retardation,
  - uncontrolled movements, } Uric Acid Crystals in CNS
  - S62}elf-mutilation

- **Adenosine deaminase deficiency** (AR)
  - Adenosine deaminase Deficiency
  - Severe combined immunodeficiency

- **Purine nucleoside phosphorylase** (AR)
  - Purine nucleoside Phosphorylase deficiency
  - Severe viral infections due to impaired

- **Hereditary orotic aciduria** (AR)
  - Orotate phosphoribosyltransferase Deficiency
  - Orotidine 5'-phosphate Decarboxylase Deficiency
  - Megaloblastic anaemia in the first year of life,
  - Failure to thrive,
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl malonic Acidemia.</td>
<td>Methyl malony COA mutase.</td>
</tr>
<tr>
<td>Propionic Acidemia.</td>
<td>Propionyl COA Carboxylase.</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency.</td>
<td>Malfunction of all carboxylase.</td>
</tr>
<tr>
<td>Ketothiolase deficiency.</td>
<td>2 methylacetyl COA thiolase def.</td>
</tr>
</tbody>
</table>
Organic Acidemia (OA)

• The term "organic acidemia" or "aciduria" applies to a group of disorders characterized by the excretion of non-amino organic acids in urine.
• Well at birth and for the first few days of life.
• Toxic encephalopathy.
• Difficult to differentiate in acute presentation
• All are autosomal recessive,
ORGANIC ACIDEMIA

Disorder
- Methyl malonic Acidemia.
- Propionic Acidemia.
- Multiple carboxylase deficiency.
- Ketothiolase deficiency.

Enzyme
- Methyl malony COA mutase.
- Propionyl COA Carboxylase.
- Malfunction of all carboxylase.
- 2 methylacetyl COA thiolase def.
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Distinctive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionic acidemia</td>
<td>Ketosis, acidosis, hyperammonia, neutropenia</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>Sweaty feet odor, acidosis</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Ketosis, acidosis, hyperammonia, neutropenia</td>
</tr>
<tr>
<td>3-methylcrotonyl-CoA carboxylase deficiency</td>
<td>Metabolic acidosis, hypoglycemia</td>
</tr>
<tr>
<td>HMG-CoA lyase deficiency</td>
<td>Reye syndrome, acidosis, hyperammonia, hypoglycemia, no ketosis</td>
</tr>
<tr>
<td>Ketothiolase deficiency</td>
<td>Acidosis, ketosis, hypoglycemia</td>
</tr>
<tr>
<td>Glutaric acidemia type I</td>
<td>No acidosis; basal ganglia injury with movement disorder</td>
</tr>
</tbody>
</table>
Organic Acid Disorders

• **Methylmalonic acidaemia**  AR
  – Methylmalonyl-CoA mutase
  – Hypotonia, Poor feeding, Acidosis,
  – Developmental delay

• **Propionic acidaemia**  AR
  – Propionyl-CoA carboxylase
  – Poor feeding, Failure to thrive, Vomiting,
  – Acidosis, Hypoglycemia
Copper Metabolism

• **Wilson** AR ATPase
  – membrane copper
  – Spasticity, Rigidity, Dysphagia, Cirrhosis
  – Transport protein ;

• **Menkes' disease** XR ATPase
  – membrane copper
  – Failure to thrive, Neurological deterioration
  – Transport protein
There are a number of disorders of steroid metabolism which can lead to virilization of a female fetus due to a block in the biosynthetic pathways of cortisol as well as a disorder of salt loss due to deficiency of aldosterone.
Steroid Metabolism

• Congenital adrenal hyperplasia  AR
• Virilization ( any new born female with ambiguous genitalia )
• **Salt-losing**
  – 21-hydroxylase  Most common (90%)
  – 11,13-hydroxylase,
  – 3 13-dehydrogenase
  – 17a-hydroxylase, very rare
  – 17,20-lyase. Very rare
• **Testicular feminization**
  – Androgen receptor
  – Female external genitalia,
  – Male internal genitalia,
  – Male chromosomes
Optimal Path to Diagnosis

Clinical Suspicion

- Finding of a unique sign or symptom
- Presentation of a cluster of common signs and symptoms

Urgent Referral

- To a geneticist or metabolic specialist

Definitive Diagnosis

- Enzyme assay diagnostic test ("gold standard")
- DNA testing
Guthrie Test--1961
MANAGEMENT OF IEM

**Genetic:**

- Establish diagnosis.
- Carrier testing.
- Pedigree analysis, risk counseling.
- Consideration of Prenatal diagnosis for pregnancies at risk.
Dependent on diagnosis and severity:

1. Dietary or vitamin therapy.
2. Drug therapy.
3. BMT.
4. Avoid known environmental triggers.
5. Surgery.
- Family counseling and support.

- Education to promote increased compliance with special form of therapy such as Protein-restricted diet.

- Assessment of community resources and support groups.
<table>
<thead>
<tr>
<th>Group I . Disorders involving COMPLEX molecules .</th>
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<tr>
<td>Lysosomal disorders.</td>
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<td>Peroxisomal disorders .</td>
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<tr>
<td>Disorders of intracellular trafficking &amp; processing .</td>
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<td>Disorders of Cholesterol synthesis</td>
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<th>Group II . Disorders that give rise to INTOXICATION .</th>
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<tr>
<td>Aminoacidopathies .</td>
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<tr>
<td>Congenital Urea Cycle Defects .</td>
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<th>Group III . Disorders involving ENERGY METABOLISM</th>
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<tr>
<td>Glycogenoses (glycogen storage disease ) .</td>
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<tr>
<td>Gluconeogenesis defects .</td>
</tr>
<tr>
<td>Fatty Acid Oxidation defects .</td>
</tr>
<tr>
<td>Mitochondrial respiratory-chain disorders .</td>
</tr>
</tbody>
</table>
What’s that smell?

- **Musty or Mousy:**
  - PKU
  - **Boiled Cabbage**
  - Tyrosinemia or hypermethioninemia
- **Maple Syrup**
  - maple syrup urine disease
- **Sweaty feet:**
  - isovaleric acidemia or glutaric acidemia type II
- **Cat urine**
  - multiple carboxylase deficiencies (Biotin deficiency)
# Quick References:

<table>
<thead>
<tr>
<th>MA: *metabolic acidosis</th>
<th>NH4:</th>
<th>Glu:</th>
<th>Dz: *Non-ketotic Hyperglycine</th>
<th>*Urea Cycle defects</th>
<th>*Fatty Acid Oxys *OAemia</th>
<th>*OAemia</th>
<th>*OAemia</th>
<th>*OAemia</th>
<th>*Glycogen Strg dfc</th>
<th>*Amino Aciduris</th>
<th>*Carb Metabolism dfc</th>
</tr>
</thead>
</table>
## Major Inborn Errors of Metabolism Presenting in the Neonate as an Acute Encephalopathy

<table>
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<tr>
<th>Disorders</th>
<th>Characteristic Laboratory Findings</th>
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<tbody>
<tr>
<td>Organic acidemias (includes MMA, PA, IVA, MCD and many less common conditions)</td>
<td>Metabolic acidosis with increased anion gap; variably elevated plasma ammonia and lactate; abnormal urine organic acids</td>
</tr>
<tr>
<td>Urea cycle defects</td>
<td>Variable respiratory alkalosis; no metabolic acidosis; markedly elevated plasma ammonia; elevated orotic acid in OTCD; abnormal plasma amino acids</td>
</tr>
<tr>
<td>Maple syrup urine disease</td>
<td>Metabolic acidosis with increased anion gap; elevated plasma and urine ketones; positive ferric chloride test; abnormal plasma amino acids</td>
</tr>
<tr>
<td>Nonketotic hyperglycinemia</td>
<td>No acid-base or electrolyte abnormalities; normal ammonia; abnormal plasma amino acids</td>
</tr>
<tr>
<td>Molybdenum co-factor deficiency</td>
<td>No acid-base or electrolyte abnormalities; normal ammonia; normal amino and organic acids; low serum uric acid; elevated sulfites in urine</td>
</tr>
</tbody>
</table>

Abbreviations: MMA, methylmalonic acidemia; PA, propionic acidemia; IVA, isovaleric acidemia; MCD, multiple carboxylase deficiency; OTCD, ornithine transcarbamylase deficiency.
## Inborn Errors of Metabolism Associated With Neonatal Liver Disease and Laboratory Studies Useful in Diagnosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Laboratory Studies</th>
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<tr>
<td>Galactosemia</td>
<td>Urine reducing substances; RBC galactose-1-phosphate uridyl transferase</td>
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<tr>
<td>Hereditary tyrosinemia</td>
<td>Plasma quantitative amino acids; urine succinylacetone a1-Antitrypsin deficiency</td>
</tr>
<tr>
<td></td>
<td>Quantitative serum a1-antitrypsin; protease inhibitor typing</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>Serum ferritin; liver biopsy</td>
</tr>
<tr>
<td>Zellweger syndrome</td>
<td>Plasma very long-chain fatty acids</td>
</tr>
<tr>
<td>N-Pick disease type C</td>
<td>Skin biopsy for fibroblast culture; studies of cholesterol esterification and accumulation</td>
</tr>
<tr>
<td>GSD type IV</td>
<td>Liver biopsy for histology and biochemical analysis or skin biopsy with assay of branching enzyme in cultured fibroblasts</td>
</tr>
</tbody>
</table>