Inborn Error Of Metabolism

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MGL-9
July 6th 2014
Genetic diseases

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

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

- **Multifactorial disorders**
Inborn Error Of Metabolism

Definition of IEM

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
What Are Inborn Errors of Metabolism?

Genetic Disorders that affect the metabolism of food.

- There are missing or defective enzymes necessary to metabolize the food eaten.
- Generally they are autosomal recessive traits.
- Food not broken down properly may produce chemicals that build up in various parts of the body causing medical problems and learning disorders.
Central Dogma of Genetics

- DNA
- RNA
- Protein

- Replication
- Reverse Transcription
- Transcription
- Translation

aa aa aa aa aa aa
- Chemical Individuality
  Garrod 20th Century
  Developed “Inborne Error of Metabolism”

- Beadle & Tatum
  Developed one gene one enzyme concept
Inborn Errors of Metabolism

a genetic disease
also known as biochemical genetics

Gene-level

Gene mutation

Protein-level

Abnormal protein

Metabolic-level

Enzyme

Abnormal metabolites

Transport protein

Other protein
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

- Need factors to break them
- Need close interactions
- Excess is like deficiency
**Basic Idea**

- Complex compound (Glycogen)
- Intermediate substance (tyrosine)
- Simple molecules (propionic A)
- Energy (Glucose)

- Enzyme Co-Enzyme
- Accumulate
- Organomegaly, Storage diseases
- Toxic
- Energy defects

- Deficiency
**What is a metabolic disease?**

<table>
<thead>
<tr>
<th>Small molecule disease</th>
<th>Organelle disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>Lysosomes</td>
</tr>
<tr>
<td>Protein</td>
<td>Mitochondria</td>
</tr>
<tr>
<td>Lipid</td>
<td>Peroxisomes</td>
</tr>
<tr>
<td>Nucleic Acids</td>
<td>Cytoplasm</td>
</tr>
</tbody>
</table>
Types of Inborn Errors

- **Protein Disorders**
  - Amino Acid
  - Organic
  - Urea Cycle

- **Carbohydrate Disorders**
  - Galactose, Glucose transport, Glycogen, Fructose

- **Fatty Acid Disorders**
  - Medium chain acyl-CoA dehydrogenase def.
  - Long chain 3 hydroxycayl-CoA dehydrogenase def.
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.
Inborn Errors of Carbohydrate Metabolism

- Carbohydrates are important energy stores, fuels and metabolic intermediates.
- Routine biochemistry tests e.g. lactate, glucose and second-line metabolic tests e.g. amino acids are essential for the investigation of disorders of carbohydrate metabolism. However, definitive diagnosis is usually achieved by measurement of the activity of the affected enzyme.
- The easiest sample type to obtain is blood (erythrocytes, leucocytes, lymphocytes) but the choice of tissue depends on the pattern of expression of the enzyme in question. For some assays, cultured skin fibroblasts (from a punch biopsy) or liver/muscle biopsies are required.
Inborn Errors of Carbohydrate Metabolism

- Galactosaemia
- Glycogen storage diseases
- Pyruvate carboxylase deficiency
- Fructose-1,6-bisphophatase deficiency
- Hereditary fructose intolerance
- Glucose-6-phosphate dehydrogenase deficiency
Galactosemia

- Results from a disturbance in the conversion of galactose to glucose
- The enzyme deficiency causes an accumulation of galactose in body tissues.
- Classic type lacks Galactose-1-phosphate uridyl transferase (GALT)

**Two types:**
- Galactokinase (GALK) deficiency results in infantile cataracts from accumulation of galacticol
- Galactose epimerase (GALE) deficiency mostly confined to blood cells and most appear normal

- Estimated incidence 1/50,000 births
**Metabolism of Galactose**

Lactose → Lactase → Galactose → Galactokinase → Galactose-1-phosphate → Uridyl transferase → Glucose

- **Brain**
  - MR

- **Liver**
  - Jaundice
  - Hepatomegaly
  - Cirrhosis

- **Eyes**
  - Chataract
Glycogen Storage Diseases

- This presents with lactic acidosis, neurological dysfunction (seizures, hypotonia, coma)
- It is a defect in the first step of gluconeogenesis which is the production of oxaloacetate from pyruvate. In addition to the effect on gluconeogenesis, lack of oxaloacetate affects the function of the Krebs cycle and the synthesis of aspartate (required for urea cycle function).
- In the acute neonatal form the lactic acidosis is severe, there is moderately raised plasma ammonia, citrulline (& alanine, lysine, proline) and ketones. Fasting results in hypoglycaemia with a worsening lactic acidosis.
- The diagnosis can be confirmed by assay of pyruvate carboxylase activity in cultured skin fibroblasts
- Patients rarely survive >3 months in the severe form
Glycogen Storage Diseases

Uridine-Diphosphogluucose

1. Glycogen synthetase
2. Brancher enzyme (GSD-IV)
3. Debrancher enzyme (GSD-III)
4. Glucose-6-phosphatase (GSD-1)

Glycogen
Straight chains

Glycogen
Branched structure

Limit dextrin + Glucose-1-PO4

Glycogen (normal branch) + Glucose

Glucose-1-PO4
# Glycogen Storage Diseases

<table>
<thead>
<tr>
<th>Disorder (approximate % GSD cases)*</th>
<th>Enzyme defect</th>
<th>Most affected tissue(s)</th>
<th>Clinical Features</th>
<th>Diagnostic tests</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD II (Pompe’s) (15%)</td>
<td>Lysosomal α1,4-glucosidase</td>
<td>Generalised; accumulation of glycogen in lysosomes</td>
<td>Infantile form: cardiomegaly, hypotonia; Juvenile &amp; adult form: skeletal myopathy</td>
<td>Enzyme assay</td>
<td>Leucocytes (with inhibitor)</td>
</tr>
<tr>
<td>GSD III (24%)</td>
<td>Debranching enzyme</td>
<td>Liver &amp; muscle (IIIa), liver only (IIIb); storage of large amounts of abnormal glycogen with short outer branches</td>
<td>Hepatomegaly, hypoglycaemia, hyperlipidaemia, growth retardation, muscle weakness</td>
<td>Enzyme assay (&amp; red cell glycogen concentration)</td>
<td>Leucocytes</td>
</tr>
<tr>
<td>GSD IV (3.3%)</td>
<td>Branching enzyme</td>
<td>Liver; accumulation of glycogen with fewer branch points and longer chains (poor solubility)</td>
<td>Hepatosplenomegaly, failure to thrive, liver cirrhosis</td>
<td>Enzyme assay</td>
<td>Leucocytes</td>
</tr>
</tbody>
</table>
### Glycogen Storage Diseases

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</thead>
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<tr>
<td>GSD V</td>
<td>Muscle phosphorylase</td>
<td>Muscle; Increased amount of glycogen (normal structure)</td>
<td>Exercise intolerance with muscle cramps</td>
<td>Mutation analysis for common mutations, Ischaemic lactate-ammonia test (and/or enzyme assay)</td>
<td>Blood DNA sample or Muscle biopsy for enzyme assay</td>
</tr>
<tr>
<td>McArthur’s (2.4%)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GSD VI</td>
<td>Liver phosphorylase</td>
<td>Liver; Increased amount of glycogen (normal structure)</td>
<td>Hepatomegaly, growth retardation, mild tendency to hypoglycaemia, mild hyperlipidaemia</td>
<td>Enzyme assay</td>
<td>Leucocytes</td>
</tr>
<tr>
<td>(see IX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSD VII</td>
<td>Phosphofructokinase</td>
<td>Muscle, erythrocytes (excess glucose leads to increased formation of glycogen)</td>
<td>Exercise intolerance, haemolytic anaemia</td>
<td>Enzyme assay</td>
<td>Muscle biopsy</td>
</tr>
<tr>
<td>(0.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSD IX</td>
<td>Phosphorylase b kinase</td>
<td>Liver and/or muscle</td>
<td>As for GSD VI (functional deficiency of phosphorylase)</td>
<td>Enzyme assay</td>
<td>Erythrocytes for X-linked liver form (muscle biopsy for muscle form)</td>
</tr>
</tbody>
</table>
Glucose-6-phosphate dehydrogenase deficiency

- This is an X-linked defect, irreversible step of the pentose phosphate pathway.

- Female heterozygotes may have symptoms but the severity varies due to non-random X chromosome inactivation.

- The highest frequency is in Mediterranean, Asian and Africans.
Glucose-6-phosphate dehydrogenase deficiency

- The most common manifestations are early neonatal unconjugated jaundice and acute hemolytic anemia. They are usually clinically asymptomatic in general.
- The hemolytic crises are usually in response to an exogenous trigger such as certain drugs (e.g. antimalarials), food (broad beans) or an infection.
- The diagnosis is by measurement of the enzyme activity in erythrocytes.
HEREDITARY FRUCTOSE INTOLERANCE: Fructose 1 phosphate aldolase deficiency

- **Diagnosis**: Fructose in Urine + Enzyme in the intestine mucosa and liver bx
- **Clinical**: Mild to sever
- **Treatment**: Diet restriction
DISORDERS OF AA METABOLISM

- PHENYLKETONURIA
- ALKAPTONURIA
- OCULOCUTANEOUS ALBINISM
- HOMOCYSTINURIA
- BRANCHED AMINOACIDS
History and Diagnosis

• PKU was discovered in 1934 by Dr. A Folling in Sweden by identifying phenylpyruvic acid in the urine of two siblings who were mentally retarded.

• 1950’s Jervis discovered a deficiency of the enzyme phenylalanine dehydrogenase in the liver tissue of an affected patient.

• 1955- Bickel demonstrated that restricting dietary phenylalanine lowers the blood concentration of phenylalanine.
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.

- **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

PA Hydroxylase D

Phenylalanine

Tyrosine

Tyrosinosis

2,5-dihydroxyphenylpyruvic acid

Homogentisic acid

Alkaptonuria

CO₂ + H₂O

Melanin

Albinism

Dietary Protein

Phenylketonuria

Phenylpyruvic acid

Tyrosinase

Chemical structures and reactions related to phenylketonuria and its metabolic pathways.
Phenylalanine Metabolism

- Phenylalanine
- Essential AA
- Major interconversions through tyrosine
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
    - Dihydropteridin 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
Guthrie Test-1961

1965 - Screening for PKU was mandated legislatively in most of the states in US
Plasma Amino Acid Profile, PKU

Low tyrosine

High phe
Treatment

- Low phenylalanine diet
  - requires careful monitoring
  - risk of tyrosine insufficiency
  - risk vitamin and trace element deficiencies

- Biopterin supplementation (sapropterin)

- Large Neutral Amino Acids (val, leu, ileu) supplements
- Diet for life
- Management of PKU pregnancies
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
Patients may display painless bluish darkening of the outer ears, nose and whites of the eyes. Longer term arthritis often occurs.
Alkaptonuria - Biochemistry

- Alkaptonuria reflects the absence of homogentisic acid oxidase activity.
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
Natural History of Classical Homocystinuria

• Lens dislocation:
  – 82% dislocated by age 10 years

• Osteoporosis (x-ray):
  – 64% with osteoporosis by age 15 yrs

• Vascular events:
  – 27% had an event by age 15 years

• Death:
  – 23% will not survive to age 30 years

• Mental Retardation – approx 50%
Branched Chain Amino Acids

- 40% of preformed AA used by mammals are BCAA Valine, Leucine, Isoleucin
- Energy supply through $\alpha$-ketoacid decarboxylase 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 (MSUD) AR

• Involves the Branch-chain amino acids:
  • Leucine
  • Iso-leucine
  • Valine

• Incidence is 1:200,000
  • Infants appear normal at birth. By four days of age they demonstrate poor feeding, vomiting and lethargy.
  • Urine has a characteristic sweet, malty odor toward the end of the first week of life

• **Treatment:** Formulas low in the branch chain amino acids
UREA CYCLE DISORDERS

• UC main function to prevent accumulation of $N_2$ waste as urea
• UC responsible for de novo arginine synthesis
• UC consists of 5 major biochemical reactions, defects in humans:
  - Carapamyl phosphate synthetase (CPS), AR
  - Ornithin transcarbamylase (OTC), X-linked
  - Argininosuccinic acid synthetase (ASA), AR
  - Argininosuccinase (AS), AR
  - N-acetyl glutamate synthetase (NAGS), AR
UREA CYCLE DISORDERS

1. Carbamyl Phosphatase Deiciency
   - Carbamyl phosphate → ornithine

2. Transcarbamylase D
   - Ornithine → citrulline

3. Argininosuccinase Synthetase A
   - Citrulline → aspartic acid

4. AS aciduria
   - Argininosuccinic acid → fumaric acid

5. Hyperarginemia
   - Arginine → ornithine

- NH₃
- HCO₃⁻
- ATP
UREA CYCLE DISORDERS

Characteristics

• Neonatal period or anytime
• Wide inter and intra familial variations in the severity of the disease,
• Lethargy, coma. Arginase deficiency cause progressive spastic quadriplegia and Mental retardation
• No acidosis (respiratory alkalosis)
• No ketones (unlike organic acidemia)
• No hypoglycemia
• But there is hyperammonemia
Cystinuria AR

• Characterized by the formation of cystine (cysteine-S-Scysteine) stones in the kidneys, ureter, and bladder.

• Cause of persistent kidney stones, due to defective transepithelial transport of cystine and dibasic amino acids in the kidney and intestine.
Lipid Metabolism

- Backbone of phospholipide 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 ACIDS

1. Long Chain
2. Medium Chain
3. Short Chain
Medium Chain Acyl-CoA Dehydrogenase

- Most common MCAD characterized by Episodic hypoglycemias provoked by fasting.
- Child with MCAD present with Vomiting and lethargy
- No ketonbodies
- Cerebral edema and encephalopathy (Glucose, no fasting)

**GENETICS:**
- Misscence mutation A → G results in substitution of glucose for lysine
- Insertion
- Deletion

**DIAGNOSIS:** DNA analysis in the newborn
**Long Chain Acyl-CoA Dehydrogenase**

- **LCAD** patients are presented with
  - Fasting induced coma
  - Hepatomegaly
  - Cardiomegaly
  - Muscle weakness
  - Hypotonia
  - Peripheral neuropathy

- Clinical and biochemical characteristics can be differentiated from each other.

- **SCAD**: Very few cases are reported with variable presentation
LDL Receptor Pathway and Regulation of Cholesterol Metabolism
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 at birth and for the first few days of life.
- Toxic encephalopathy.
- Difficult to differentiate in acute presentation.
- All are autosomal recessive, the commonest Methylmalonic acidemia MMA.,
## Organic Acidemia, Disorders of OA

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Distinctive features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propionic acidemia</td>
<td>Ketosis, acidosis, hyperamm neutropenia</td>
</tr>
<tr>
<td>Isovaleric acidemia</td>
<td>Sweaty feet odor, acidosis</td>
</tr>
<tr>
<td>Methylmalonic acidemia</td>
<td>Ketosis, acidosis, hyperamm 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, hyperamm, 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 acidemia

Clinically:
- Healthy NB → rapidly ill, Ketoacidosis, poor feeding
- Vomiting, dehydration
- Hypotonia, lethargy
- Tachypnea, seizures
- Coma, unusual odors
- Pancreatitis, cardiomyopathy, infection (recurrent).

Lab diagnosis
- Metabolic acidosis
- Hyperammonemia
- Hypoglycemia
- Lactic acidosis
- Anemia, ± thrombocytopenia ± neutropenia
- Definite diagnosis, Tandem MS & Urine organic acid analysis
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.
Mucopolysaccharides (glycosaminoglycans) are found in bone, connective tissue, skin, cornea, joints, etc. Cell membranes, organelles, bacteria, viruses, and glycoproteins also contain these compounds.

Glycogen is another important carbohydrate found in lysosomes.

Food particles, sphingolipids, glycolipids, and acid hydrolases also play a role in lysosomal functions.

Abnormal lysosomal storage leads to developmental regression.

Lysosomes are often referred to as "the cells wrecking crew."
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
## LIPIDOSES

<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>Hexosamindase A</td>
</tr>
<tr>
<td>Sandhoff disease.</td>
<td>Hexosamindase 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>
Sphingolipidoses

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

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

• **Niemann-Pick disease**  
  - AR  
  - Sphingomyelinase  
  - Failure to thrive, Hepatomegaly  
  - Cherry-red spot, Developmental
Mucopolysaccharidosis

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

• Hunter syndrome
• Hurler syndrome
• Scheie syndrome
• Sanfilippo syndrome
• Morquio disease
• Maroteaux-Lamy syndrome
Cystinosis AR

- 1/200,000 births
- Lysosomal storage disease due to impaired transport of cystine out of lysosomes.
- High intracellular cystine content. Crystals in many tissues. Clinical Manifestations are age dependent include renal tubular Fanconi syndrome, growth retardation (Infancy syndrome), Renal failure develops by 10 year of year (Late childhood) and cerebral calcification (adolescence period).
Purine/pyrimidine metabolism

- **Lesch-Nyhan disease**
  - XR
  - Hypoxanthine Guanine Phosphoribosyltransferase Deficiency
  - Mental retardation,
  - uncontrolled movements, } Uric Acid Crystals in CNS
  - S64}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,
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
Steroids Metabolism

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.

1: 17-hydroxylase deficiency
2: 3β dehydrogenase
3: 11β dehydrogenase
4: Androgen insensitivity
Steroid Metabolism

- Congenital adrenal hyperplasia  AR
- Virilization ( any new born female with ambiguous genitalia )
- **Salt-losing**
  - 21-hydroxylase  Most common (90%)
  - 11,13-hydroxy!ase,
  - 3 13-dehydrogenase
  - 17a-hydroxylase,  very rare
  - 17,20-lyase. Very rare
- **Testicular feminization**
  - Androgen receptor
  - Female external genitalia,
  - Male internal genitalia,
  - Male chromosomes
Every child with unexplained . . .

- Neurological deterioration
- Metabolic acidosis
- Hypoglycemia
- Inappropriate ketosis
- Hypotonia
- Cardiomyopathy
- Hepatocellular dysfunction
- Failure to thrive

. . . should be suspected of having a metabolic disorder
What to do for the Dying Infant Suspected of Having an IEM

- Autopsy--pref. performed within 4 hours of death
- Tissue and body fluid samples
  - Blood, URINE, CSF (ventricular tap), aqueous humour, skin biopsy, muscle and liver--frozen in liquid nitrogen
- Filter paper discs from newborn screen--call lab and ask them not to discard
Laboratory Studies For an Infant Suspected of Having an Inborn Error of Metabolism

- Complete blood count with differential
- Urinalysis
- Blood gases
- Serum electrolytes
- Blood glucose
- Plasma ammonia
- Urine reducing substances
- Urine ketones if acidosis or hypoglycemia present
- Plasma and urine amino acids, quantitative
- Urine organic acids
- Plasma lactate
SUMMARY
# Major Inborn Errors of Metabolism Presenting in the Neonate as an Acute Encephalopathy

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

Abbreviations: MMA, methylmalonic acidemia; PA, propionic acidemia; IVA, isovaleric acidemia; MCD, multiple carboxylase deficiency; OTCD, ornithine transcarbamylase deficiency.
<table>
<thead>
<tr>
<th>Group I . Disorders involving COMPLEX molecules .</th>
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<tbody>
<tr>
<td>Lysosomal 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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<tr>
<th>Group II . Disorders that give rise to INTOXICATION .</th>
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<tr>
<td>Aminoacidopathies .</td>
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<td>Congenital Urea Cycle Defects .</td>
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<td>Organic acidemias .</td>
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<td>Sugar intolerances .</td>
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<tr>
<th>Group III . Disorders involving ENERGY METABOLISM .</th>
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<tbody>
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<td>Glycogenoses (glycogen storage disease) .</td>
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<tr>
<td>Gluconeogenesis defects .</td>
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<tr>
<td>Congenital Lactic Acidemia .</td>
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<tr>
<td>Fatty Acid Oxidation defects .</td>
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<tr>
<td>Mitochondrial respiratory-chain disorders .</td>
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<tr>
<td>Disorder</td>
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<tr>
<td>Galactosemia</td>
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<td>Hereditary tyrosinemia</td>
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<tr>
<td>Neonatal hemochromatosis</td>
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<tr>
<td>Zellweger syndrome</td>
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<tr>
<td>N-Pick disease type C</td>
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<tr>
<td>GSD type IV</td>
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