INBORN ERRORS OF METABOLISM
(IEM)
OBJECTIVES

• What are IEMs?
• Categories
• When to suspect?
• History and clinical pointers
• Metabolic presentation
• Differential diagnosis
• Emergency and long term management
• Expanded newborn screening
WHAT ARE IEMS?

• Monogenic disorders primarily Autosomal Recessive resulting from deficiency of:

  - A critical enzyme in the intermediary pathways of carbohydrate, protein and lipid metabolism

  or

  - A co-factor which is responsible for activation of an apoenzyme in the same pathways
WHAT ARE IEMS?

Clinical effects result from:

• Lack of the product
• Accumulation of immediate and remote precursors/toxic byproducts
• Secondary metabolic consequences
IEMS: A FORMIDABLE CHALLENGE

- Number and Complexity
- Diverse clinical manifestations
- Mimic many common pediatric illnesses including sepsis, encephalopathy
- Limited availability of lab services
- Emergency and long term care
- Counseling
CATEGORIES OF IEM

• Carbohydrate
  - Oxidative phosphorylation (OXPHOS) disorders
  - Glycogen storage disorders, Galactosemia

• Protein
  - Urea cycle disorders
  - Organic acidemias
  - Aminoacidopathies

• Lipids
  - Fatty acid oxidation disorders (FAOD)
  - Disorders of carnitine transport
CATEGORIES OF IEM

• Lysosomal storage disorders (LSD):
  - Mucopolysaccharidosis (MPS), sphingolipidosis

• Peroxisomal disorders

• Mitochondrial disorders
CASE ILLUSTRATION

• A 6 month old male, 2nd order, born of non consanguinity, admitted for diarrhoea and dehydration
• H/O Sibling death with suspected Reye syndrome (encephalopathy)
• No developmental delay/ failure to thrive
• O/E: Moderate dehydration, rapid breathing, drowsy
• Hepatomegaly, firm, span 8cm
WHEN TO SUSPECT IEM?
CLINICAL POINTERS - HISTORY

• Developmental delay (DD), regression, mental retardation (MR)
• Refractory seizures
• Encephalopathy
• Rapid breathing (Acidotic)
• Failure to thrive, episodic vomiting
• Unusual body odours
• Life threatening illnesses following seemingly minor infections
• Consanguinity, family history of sibling deaths, DD/MR, seizures
# ABNORMAL URINARY ODOURS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Odor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylketonuria</td>
<td>Musty</td>
</tr>
<tr>
<td>Maple Syrup Urine Disease (MSUD)</td>
<td>Maple syrup or burnt sugar</td>
</tr>
<tr>
<td>Isovaleric acidemia, Glutaric acidemia type 2</td>
<td>Sweaty feet</td>
</tr>
<tr>
<td>Multiple carboxylase deficiency</td>
<td>Cat urine</td>
</tr>
</tbody>
</table>
WHEN TO SUSPECT IEM?
CLINICAL POINTERS - EXAMINATION

• Cataract, corneal clouding, cherry red spot
• Micro/ Macrocephaly, coarse facies
• Alopecia, intertrigo
• Hepatomegaly, liver dysfunction
• Splenomegaly
• Abnormal CNS examination
• Skeletal deformities
# CLINICAL POINTERS TO DIAGNOSE IEM

<table>
<thead>
<tr>
<th>Feature</th>
<th>disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye</strong></td>
<td><strong>Galactosemia</strong>&lt;br&gt;<strong>MPS: Hurler, Scheie, Morquio, Maroteaux-Lamy syndrome</strong>&lt;br&gt;<strong>Tay-Sachs, Niemann Pick</strong></td>
</tr>
<tr>
<td>Cataract&lt;br&gt;Corneal clouding</td>
<td><strong>Cherry red spot</strong>&lt;br&gt;<strong>Galactosemia</strong>&lt;br&gt;<strong>MPS: Hurler, Scheie, Morquio, Maroteaux-Lamy syndrome</strong>&lt;br&gt;<strong>Tay-Sachs, Niemann Pick</strong></td>
</tr>
<tr>
<td>Cherry red spot</td>
<td><strong>Skin - Alopecia, intertrigo</strong>&lt;br&gt;<strong>Hair – Coarse, kinky</strong>&lt;br&gt;<strong>Biotinidase deficiency</strong>&lt;br&gt;<strong>Menkes kinky hair disease</strong></td>
</tr>
<tr>
<td><strong>Skin - Alopecia, intertrigo</strong>&lt;br&gt;<strong>Hair – Coarse, kinky</strong></td>
<td><strong>Hepato ± splenomegaly</strong>&lt;br&gt;<strong>LSD: MPS, sphingolipidosis, GSD</strong></td>
</tr>
<tr>
<td><strong>Hepato ± splenomegaly</strong></td>
<td><strong>Hepatomegaly &amp; liver dysfunction</strong>&lt;br&gt;<strong>Galactosemia, tyrosinemia, GSD</strong></td>
</tr>
<tr>
<td><strong>Hepatomegaly &amp; liver dysfunction</strong></td>
<td><strong>Cardiomyopathy</strong>&lt;br&gt;<strong>LSD, GSD, FAOD, mitochondrial disorders</strong></td>
</tr>
</tbody>
</table>
CASE ILLUSTRATION: INVESTIGATIONS

- GRBS: 45 mg/dl; Urine ketones: Positive
- ABG: pH 7.09, pCO2 14.8, BE – 23.6, HCO3 4.5
- Metabolic acidosis
- Anion gap 33 - Wide
- NH3 328 µg/dl (N: 25-94) - Hyperammonemia
- Lactate 28.8 mg/dl (N: 2.5-20) – Lactic acidosis

- FINAL DIAGNOSIS – ORGANIC ACIDEMIA
WHEN TO SUSPECT IEM?
LAB POINTERS

• Metabolic acidosis
• Wide anion gap
• Hyperammonemia
• Hypoglycemia:
• Urine Ketones (Ketotic/ non ketotic)
• Urine Reducing substances (Positive/ Negative)
• Lactic acidosis
• Altered liver function
Hyperammonemia

Absent

Metabolic Acidosis

Absent

Amino acid disorders

No Ketonuria

Fatty Acid Oxidation disorders

Lactic Acidosis

OXPHOS disorders

Ketosis

Organic Acidemias GSD

Urea Cycle disorders

Metabolic Acidosis

Present

Hypoglycemia

Absent

Metabolic Acidosis

Present
DEFINITIVE DIAGNOSIS

• Blood: Tandem mass spectrometry for acyl carnitine, organic acids
• Plasma and urine amino acids (quantitative)
• Urine organic acids by chromatography
• Specific metabolite assays
• DNA mutation analysis
• Enzyme assays on skin fibroblasts or blood cells
Differential Diagnosis

• Sepsis:
  - Can mimic, precipitate and complicate IEM
  - Galactosemia – predilection for E coli sepsis
  - Negative CRP and blood culture in a rapidly deteriorating infant should alert to possible IEM

• Reye encephalopathy
  - An important differential for FAOD with hepatomegaly, hypoglycemia, hyperammononemia and hepatic dysfunction
MANAGEMENT GOALS

- Prevention of formation of toxic metabolites
- Removal of toxic metabolites
- Increase activity of deficient enzyme by co-factor therapy (Mega vitamins)
- Addition of deficient substrate
- Supply essential nutrients/ disease specific diet
MANAGEMENT: EMERGENCY

- ABC
- Correction of hypoglycemia and maintenance of blood sugars to suppress gluconeogenesis
- Correction of acidosis: IV Sodium bicarbonate with serial ABGs
- Carnitine supplementation
- Broad spectrum antibiotics including anaerobic cover
HYPERAMMONEMIA – MANAGEMENT

• Hemodialysis for rapid reduction
• Decrease production: I.V. Arginine HCl
• Promote excretion: I.V. sodium benzoate and sodium phenyl acetate
• Calories: carbohydrate/ lipid; reintroduction of protein after 48 hours restricted to 1 g/kg with 50% essential amino acids
• Avoid valproate, steroids
<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dosage/day</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotin</td>
<td>10 - 50 mg</td>
<td>Holo carboxylase deficiency, Biotinidase</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>100 mg</td>
<td>Glutaric aciduria, Electron Transport Chain defects</td>
</tr>
<tr>
<td>Thiamine</td>
<td>300 mg</td>
<td>MSUD, Pyruvate met defects, Mitochondrial</td>
</tr>
<tr>
<td>Vit B&lt;sub&gt;12&lt;/sub&gt;</td>
<td>1 - 2 mg</td>
<td>Methyl malonic acidemia, Homocystinuria</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>50 – 100 mg</td>
<td>Dependent seizures, Homocystinuria</td>
</tr>
</tbody>
</table>
DIET MANAGEMENT

• Restriction of proteins: 6% of total energy
• Restriction of substrates which accumulate
  - Homocystinuria: Methionine
  - PKU: phenylalanine
• Special diets:
  - PKU, MSUD, galactosemia
• Replacement of deficient nutrients
  - Homocystinuria: cystein
EXPANDED NEWBORN SCREENING

• Pre-symptomatic detection of newborns that includes several IEM

• Originated with the development of the “Guthrie test” for detecting phenylketonuria

• Dried Blood Spots: Heel prick blood at 48-72 hours of age on absorbent paper (Guthrie card) and analyzed by tandem mass spectrometry
IEMS ARE:

• Individually rare but collectively have an incidence of 1 in 5000
• Presentation can occur at any age, even in adulthood
• Increasingly a primary/differential diagnosis especially in infancy
• “Index of suspicion” - The most difficult step in diagnosis is considering the possibility!
THANK YOU