Inborn Errors of Metabolism
George E Tiller, MD, PhD
Regional Chief, Dept. Genetics
Southern California Permanente Medical Group
Los Angeles, CA

Objectives of Lecture
• describe purpose and shortcomings of newborn screening
• develop an approach to diagnosing metabolic disease starting with common test results
• recognize the acute nature of metabolic disease in the newborn period
• describe presenting features of common metabolic diseases

Inborn Error of Metabolism

• a biochemical disorder caused by a genetically determined defect (usually an enzyme deficiency) in a metabolic pathway

Consequences of an Enzyme Deficiency

\[ \uparrow A \xrightarrow{\times} \downarrow B \rightarrow \uparrow C \]

\[ \downarrow D \rightarrow \uparrow E \]
Selected Inborn Errors of Metabolism

<table>
<thead>
<tr>
<th>amino acidurias</th>
<th>organic acidurias</th>
<th>urea cycle d/o</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenylketonuria</td>
<td>methylmalonic aciduria</td>
<td>OTC def. (XLR)</td>
</tr>
<tr>
<td>homocystinuria</td>
<td>maple syrup urine dz.</td>
<td>arginosuccinase def.</td>
</tr>
<tr>
<td>tyrosinemia</td>
<td>MCAD deficiency</td>
<td>citrullinemia</td>
</tr>
<tr>
<td>carbohydrate d/o</td>
<td>transport d/o</td>
<td>metal metabolic d/o</td>
</tr>
<tr>
<td>galactosemia</td>
<td>cystinuria</td>
<td>Wilson's dz.</td>
</tr>
<tr>
<td>fructose intolerance</td>
<td>cystinosis</td>
<td>Menkes' dz. (XLR)</td>
</tr>
<tr>
<td>glycogen storage d/o</td>
<td>hypercholesterolemia (AD)</td>
<td>homochromatosis</td>
</tr>
<tr>
<td>lipidoses</td>
<td>lysosomal d/o</td>
<td>peroxisomal d/o</td>
</tr>
<tr>
<td>Tay-Sachs dz.</td>
<td>Hunter sx. (MPS I)</td>
<td>ALD (XLR)</td>
</tr>
<tr>
<td>Gaucher dz.</td>
<td>Hunter sx. (MPS II;XLR)</td>
<td>Zellweger sx.</td>
</tr>
<tr>
<td>metachromatic</td>
<td>l-cell dz. (ML II)</td>
<td>chondrodysplasia</td>
</tr>
<tr>
<td>leukodystrophy</td>
<td></td>
<td>punctata</td>
</tr>
</tbody>
</table>

autosomal recessive inheritance

Clinical Presentation of IEMs

- **acute**
  - metabolic dz of newborn

- **progressive**
  - organomegaly,
  - loss of milestones

- **chronic**
  - failure to thrive,
  - mental retardation

- **late or benign**
  - transport d/o
**Principles for Newborn Screening**
- high burden to affected individual
- preventable or treatable disorder
- methods for screening, Dx, Tx practical and available to population
- inheritance and pathogenesis known
- high benefit/cost ratio
- high sensitivity and specificity of screen

**Pitfalls of Newborn Screening**
- dietary prerequisite not met
- poor communication
- mishandling sample
- mislabeling sample or forms
- false (+) results
- false (-) results
- limited access to outpatient care

**The Newborn Screening Process**
- screening card implemented in nursery
- card processed by state lab
- abnormal screen results called to MD and metabolic referral ctr.
- screen repeated +/- dx test ordered +/- diet modified
- if 2nd screen abnl, infant brought to referral center for further testing, counseling family, +/- instituting tx
Newborn Screening

• “old list”: PKU, Galactosemia, Thyroid, CAH, Hemoglobinopathies
• expanded list includes:
  amino acidopathies: Phe, Tyr, Homocys
  organic acidurias: propionic, methylmalonic
  fatty acid oxidation defects: SCAD, MCAD, VLCAD, LCHAD, CPT
  urea cycle d/o: citrullinemia

Galactosemia

• incidence: 1/60,000
• screen test: Gal; GALT assay
• prerequisite: Gal (lactose) intake
• dx test: GALT electrophoresis
• clinical: neonatal N/V/D, jaundice, hepatomegaly, hepatic dysfunction, cataracts, E. coli sepsis, death
• tx: galactose/lactose-free diet

Phenylketonuria

• incidence: 1/15,000 (commonest aa d/o)
• screen test: Phe (blood spot)
• prerequisite: protein intake >24hr
• dx test: quant plasma aa profile
• clinical: mod-severe MR, autism, seizures, hypopigmentation, eczema
• tx: low-Phe (low protein) diet for life; BH4 for mild cases
Homocystinuria

- incidence: 1/100,000
- screen test: Methionine (blood spot)
- dx test: quant. plasma aa profile
- clinical: tall stature, scoliosis, osteoporosis, mild MR, ectopia lentis, hypercoagulability
- tx: betaine, folate, and/or pyridoxine; ASA for anticoagulation

Treatment of Homocystinuria

Hypothyroidism

- incidence: 1/4,500 (genetic heterogeneity)
- screen test: T₄; TSH
- prerequisite: none
- dx test: T₄, TSH
- clinical: lethargy, FTT, eczema, macroglossia, MR
- tx: L-thyroxine (Synthroid)
Congenital Adrenal Hyperplasia

- incidence: 1/1,000 (mild form)
- inheritance: autosomal recessive
- clinical (classic): virilization of females; salt wasting (severe form)
- lab: elevated 17-OH progesterone
- 1st defect: 21-hydroxylase deficiency (90%)
- tx: hydrocortisone +/- Florinef & NaCl

Metabolic Disease of the Newborn

- individually rare
- nonspecific symptoms
- delayed diagnosis → irreversible damage

Suspicion of Acute Metabolic Disease in Infancy

- family hx neonatal deaths
- initially normal newborn
- anorexia → vomiting → lethargy → coma
- seizures
- peculiar odors
- metabolic acidosis
Lab Evaluation of Possible IEM

**readily available tests**
- CBC w/ diff & pltts
- serum glucose
- lactate/pyruvate
- electrolytes
- NH₃
- urinalysis

**esoteric ($$$) stuff**
- plasma amino acids, urine organic acids, VLCFA, acylcarnitine profile, enzyme assays

---

**MCAD Deficiency**

- **incidence:** 1/15,000
- **inheritance:** autosomal recessive
- **clinical:** predisposed to severe hypoglycemia, coma, “SIDS”
- **lab:** hypoglycemia without ketonuria; abnormal acylcarnitine profile
- **1° defect:** medium chain acyl-CoA dehydrogenase deficiency
- **tx:** frequent feeding; carnitine
Causes of Hyperammonemia

• transient hyperammonemia of the newborn
• urea cycle disorders
• organic acidemias
• “Reye syndrome”

Presentation of Urea Cycle Disorders

• neonatal >> infantile >> juvenile onset
• initially normal newborn
• anorexia → vomiting → lethargy → coma
• hyperventilation, hypothermia
Treatment of Urea Cycle Disorders

• prevent protein catabolism
  - generous caloric intake (fat, CHO)
  - arginine supplementation
• decrease NH₃ load
  - protein restriction (0.5-2.0gm/kg/d)
• utilize NH₃ scavengers
  - benzoate, phenylbutyrate, phenylacetate

Nonketotic Hyperglycinemia

• incidence: 1/200,000
• inheritance: autosomal recessive
• clinical: hiccups, neonatal seizures, coma
• lab: hyperglycinemia without ketonuria; CSF/plasma Gly >.09
• 1° defect: glycine cleavage pathway
  \[ \text{Gly} \rightarrow \text{CO}_2 + \text{NH}_3 \]
• tx: benzoate scavenges Gly; valium and dextromethorphan bind Gly receptors

Dietary Management of IEMs

*PKU*: Phe/protein restriction
*Galactosemia*: Galactose/lactose-free diet
*Fructose intolerance*: restrict fruits/juices
*Urea cycle d/o’s*: protein restriction
*Maple syrup urine dz*: restrict branch-chain amino acids/protein
*Hypercholesterolemia*: restrict fat/cholesterol
Pharmacologic Management of IEMs

**PKU:** BH₄

**Homocystinuria:** betaine, folate, ASA

**MCAD deficiency:** carnitine

**Urea cycle d/o’s:** benzoate, arginine

**MSUD:** thiamine (B₁)

**Methylmalonic aciduria:** B₁₂

**NKHG:** benzoate, valium, dextromethorphan

**Lysosomal storage disorders:** enzyme replacement therapy (Gaucher, Fabry, Pompe, MPS I & II)

---

**Gaucher Disease**

- incidence 1/5,000 Ashkenazi Jews, 1/50,000 general population
- inheritance: autosomal recessive
- multisystem disease of the RE system
- mild (I), acute neuronopathic (II), chronic neuronopathic (III) forms
- 1º defect: glucocerebrosidase deficiency
- Rx: enzyme replacement tx

---

**Successful Management of IEM**

- early detection
- early institution of tx: dietary +/- pharmacologic
- family education
- high compliance with tx regimen
- financial/social support
- periodic follow-up in metabolic center
- anticipation with acute illnesses
Metabolic References


- CI Kaye and Committee on Genetics. Introduction to the newborn screening fact sheets. Pediatrics 118:1304, 2006. (both can be found online at http://aappolicy.aappublications.org)

- info from the American College of Medical Genetics: www.acmg.net/resources/policies/ACT/condition-analyte-links.htm

- info from California Genetic Disease Branch: www.dhs.ca.gov/gh (follow link to CA Newborn Screening program)