Nutritional Management of Inborn Errors of Metabolism

Kay Davis, RD, CSP
Esther Berenhaut, RD, CSP, CSR
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OBJECTIVES

• Brief overview of newborn screening of metabolic disorders, inheritance patterns.

• Identify major macronutrients involved in inborn errors of metabolism

• Case study of an infant with an inborn error of metabolism involving protein
HISTORY OF NEWBORN SCREENING

• Dr. Asbjorg Folling

• 1934 - group of mentally retarded patients with a strange odor
  - discovered ketone in the urine
  - phenylpyruvic acid
  - Phenyl + Ketone + Nuria = PKU
HISTORY OF NEWBORN SCREENING

• Dr. Horst Bickel - 1951

• Assisted in development of the 1st amino acid-based formulas for PKU and other conditions

• Treatment needed to be started in early infancy to be effective

How do we find the babies???
NEWBORN SCREENING

• Dr. Robert Guthrie

• 1958 - created “Guthrie test”

• 1962 - first NBS pilot in Massachusetts
  - screened 53,000 babies and found 9 with PKU
    (1-6,000)

• 1966 - PKU testing mandated in most states
HISTORY OF NEWBORN SCREENING

• California NBS Program

  • 1966 - screening for PKU
  • 1980 - addition of galactosemia and congenital hypothyroidism PLUS a comprehensive follow up system
  • 1990-1999 - sickle cell screening and non sickling hemoglobin disorders
  • 2005 - expanded NBS - 40+ additional disorders
    • Amino acid disorders
    • Fatty acid oxidation disorders
    • Endocrine disorders
    • Organic acidemias
    • Urea cycle defects
  • 2007 - Biotinidase, Cystic Fibrosis
  • 2016 - Adrenoleukodystrophy
Inheritance of Metabolic Disorders

Autosomal Recessive Inheritance
Chances for each child when both parents are carriers

Carrier Father
Carrier Mother

Keys:
- R = working gene
- r = non-working gene

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Description</th>
<th>Probability</th>
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</thead>
<tbody>
<tr>
<td>RR</td>
<td>Normal</td>
<td>(25%)</td>
</tr>
<tr>
<td>Rr</td>
<td>Carrier</td>
<td>(50%)</td>
</tr>
<tr>
<td>rr</td>
<td>Has the disorder</td>
<td>(25%)</td>
</tr>
</tbody>
</table>
Inheritance of Metabolic Disorders

X-Linked Recessive Inheritance
(Carrier Mother)

Father

Carrier Mother

Normal Daughter (25%)
Normal Son (25%)
Carrier Daughter (25%)
Affected Son (25%)

Common in Urea cycle defects, some energy/glucose disorders
Simplified Metabolic Pathway

A → B → C → D

A → B → C → D
Categories of Metabolic Disease

• There are three major nutrients that are not metabolized correctly:
  
  • Protein (amino acids/organic acids/urea cycle)
  
  • Carbohydrate (glucose/galactose/fructose)
  
  • Fat (fatty acids/transport/electron transport chain)
Dietary Goal for Metabolic Patients

• Provide appropriate nutrition for growth and development with limited amounts the offending substrate as soon as possible.

• Diet therapy may vary widely depending on severity of condition
Basics of Dietary Treatment

• Fasting Avoidance - to prevent catabolism

• Formulas (medical foods) and foods that are free or reduced of offending amino acids/fats/carbohydrates

• Low protein foods (amino acid disorders)

• Medications, vitamin supplements, additional/supplemental amino acids

• Monitor growth, weight, labs to prevent excess/inadequate delivery of offending substrate.

• Life long therapy
Phenylketonuria (PKU)
Phenylketonuria (PKU)

- Most common of the amino acid disorders (now referred to as Hyperphenylalaninemia - HPA)

- 1:15,000 live births

- Autosomal recessive inheritance pattern

- Diet intervention prevents mental retardation caused by elevated serum phenylalanine (phe) levels

- Detected by Newborn Screening
STANDARD NUTRITION THERAPY

- Restrict phenylalanine (phe) - not elimination
- Supplement tyrosine (tyr)
- Implement Medical food product to supply adequate protein for growth
- Use low protein foods for additional calories and palatability
- Monitor plasma amino acids (phe level 120-360 umol/L)
- The more adherent, the better the outcome!
Alternative Treatments in PKU

- Kuvan (sapropterin dihydrochloride)
  - Cofactor with phenylalanine hydroxylase (PAH)
  - May improve PAH activity in PKU patients with known mutations

- Large Neutral Amino Acid (LNAA) Therapy
  - Blocks uptake of phe at the blood brain barrier and GI tract
  - LNAA’s include tryptophan, tyrosine, branched chains.
  - May decrease blood phe concentrations and prevent uptake by the brain.
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)

- Autosomal recessive inheritance (1:14,000)
- Most common of fatty acid oxidation defect (b-oxidation pathway - mitochondrion)
  - Medium chain fats (C8 – C10)
- Children are asymptomatic until fasted/illness (fat stores mobilized)
- Detected on NBS since 2005
MCADD

• Fatal in 25-33% of first presentation (hypoglycemia, hyperammononemia, fatty liver, coma, seizures)

• 25-33% of survivors had long term neurological issues after initial presentation
  – Cerebral Palsy
  – Learning/behavior problems

• A significant number remain asymptomatic
**MCADD**

- **Treatment - *Fasting avoidance***
  
  - No more than 4 hours in between feedings until 4 months of age (avoid high MCT containing formulas if not breast fed)
  
  - 5-12 month - add one hour per month (1/2 time for illness)
  
  - Regular meals and snacks in childhood and adulthood.
  
  - Additional carbs for exercise
  
  - No NPO for procedures - need high dextrose IVF
  
  - Monitor carnitine levels in case of deficiency
Galactosemia

- Defect in the Galactose 1 phosphate uridyltransferase gene (GALT)
Galactosemia

• Autosomal recessive inheritance

• US occurrence rate 1:18,000

• Symptoms present in first few days of life
  • Loss of appetite
  • Vomiting
  • Severe jaundice/ascites/hepatomegaly
  • Sepsis
  • +/- Catatacts
Galactosemia

• **Treatment - galactose restricted diet**
  - Stop breast feeding - lactose free formula
  - Lactose free/reduced foods
  - Foods with milk/milk components
  - Vitamin supplements/medications without lactose extenders

• **Monitoring**
  - Serum galactose 1 phosphate levels/urine galactitol levels

• **Long term issues**
  - Speech difficulties
  - Cataracts
  - Ovarian failure
Case Study

- DOB - 11/7/06
- DOS - 11/10/06 - 62 hours old
- NBS Result date - 11/12/06
- Leucine/Isoleucine = 1331 umol/L (N=0-200)
- Family contacted and child brought to CHLA ED on 11/12/06.
Case Study

• Born Full Term 7#8oz on 11/7/2006
• NICU stay for Tachypnea due to aspiration of amniotic fluid until DOL#3
• Eating normally on admission to ED on 11/12/06
• Normal smelling urine
• Plasma amino acids drawn and patient had moderate ketones
• Placed on D10 prior to admission to floor and initiating metabolic formula on 11/13/06.
• PAA levels (11/13): LEU 2657 (n47-155); VAL 861 (n64-294); ILE 794 (n31-86)
Case Study (MSUD)

- Maple Syrup Urine Disease (MSUD)
  - Genetic disorder of branched chain amino acid (BCAA) metabolism (Leucine, isoleucine and valine)
  - Autosomal recessive inheritance pattern
  - Rare Disorder - incidence 1: 185,000
  - Defect in Branched chain alpha keto acid dehydrogenase; multienzyme complex responsible for the breakdown of the BCAA’s
  - Classic (most common/severe), Intermediate, mild, and thiamin responsive forms
  - Added to NBS in 2005
Catabolism of Branched Chain Amino Acids
Case Study (MSUD)

• Infants appear normal at birth and develop symptoms between 4-7 days of life (breastfeeding delays onset until the second week)

• Initial symptoms include poor feeding and lethargy, alternating hyper and hypotonia, increased irritability.

• Patients with classic MSUD rapidly develop severe ketoacidosis with dystonia, seizures, coma and death if untreated
Case Study (MSUD)

Late diagnosis (prior to NBS)

Early Diagnosis (with NBS)
Case Study (MSUD)

- Treatment is *timely restriction* of dietary Leucine (toxic!)

- Supplementation of isoleucine and valine when appropriate (much lower toxicity/competes for uptake at GI level).

- Provision of adequate calories, protein (medical foods and solid foods) and micronutrient to maintain growth and development.

- Thiamin supplementation (initially) until mutations are determined

- Goals for therapy are Leucine levels between 150 - 300umol/L
Case Study (MSUD)

• Initially start with BCAA free formula only
  • knock down leucine levels
  • Supplement isoleucine and valine

• Provide standard formula to provide adequate BCAA to maintain weight gain/growth.

• Frequent monitoring of plasma amino acids to ensure appropriate diet.
Case Study (MSUD)

- 11/14/06 - admitted to NICU
- Developed worsening acidosis (corrected with additional glucose D35 plus insulin)
- Developed leucine encephalopathy with declining neurologic status (non alert, hiccups, tonic posturing); seizure activity noted
- 11/17 - EEG - abnormal
- 11/28 - MRI - abnormal acute necrosis involving brainstem, cerebellum, and cortical spinal tract.
Case Study (MSUD)

• Scintiscan 11/21/06 - normal
• UGI 11/22/06 - no reflux/normal anatomy
• MBSS 12/1/06 - inconclusive - considered unsafe to swallow
• PEG placement - 12/12/06
• MBSS 12/14/06 - aspiration on thin and tolerating nectar thick liquids.
• Discharged on full g-tube feeds
  • 1/2 c. + 2 tbsp MSUD Analog + 4 tbsp Enfamil +1 Tbsp Duocal to end volume 24 oz water
  • Give 3 oz of MSUD formula every three hours by g-tube.
Case Study (MSUD)

- Follow up Outpatient Visit: age 3 months

**Anthropometrics**

<table>
<thead>
<tr>
<th>Date</th>
<th>Length</th>
<th>Weight</th>
<th>L/W ratio</th>
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<tbody>
<tr>
<td>2/20</td>
<td>61.4 cm</td>
<td>6.6 kg</td>
<td>50-75%ile</td>
</tr>
<tr>
<td>1/23</td>
<td>60 cm 50%ile</td>
<td>6.1 kg 50%ile</td>
<td>50%ile</td>
</tr>
</tbody>
</table>

**Formula**

- ½ cup + 1Tbsp MSUD Analog (95 g)
- 5.5 Tbsp Similac Advance powder (48g)
- 1 Tbsp Duocal (8.5g)
- water to end volume of ~29 ounces (870 mL)
- Total kcals - 723 kcals (109/kg)
- Total protein - 17g (2.6/kg)
Case Study (MSUD)

• Biochemical
  • Leucine - 51 μMol (N = 47-155)
  • Isoleucine - 430 μMol (N = 31-86)
  • Valine - 268 μMol (N = 64-294)

• Feeding
  • Child taking all feeds orally with exception of 9am feeding.
  • Mother adding 2.75 teaspoons (13 kcals) of Thicken Up to nectar consistency with formula for each 4 ounces of formula.
Case Study (MSUD)

• What would you do?
  • Do nothing?
  • Change formula components?
  • Increase formula volume?
  • Suggestions?
Our knowledge is only the tip of the iceberg!
Resources

• NORD - national organization for rare disorders (www.rarediseases.org)
• March of Dimes (www.marchofdimes.com)
• IEM’S - www.newbornscreening.info

• Newsletters, Websites, Support Groups
  • PKU - www.pkunews.org
  • Fatty Acid Disorders- www.fod.org
  • MSUD - www.msud-support.org
  • Urea Cycle Disorder Foundation - www.nucdf.org
  • Mitochondrial Disease Foundation - www.umdf.org