

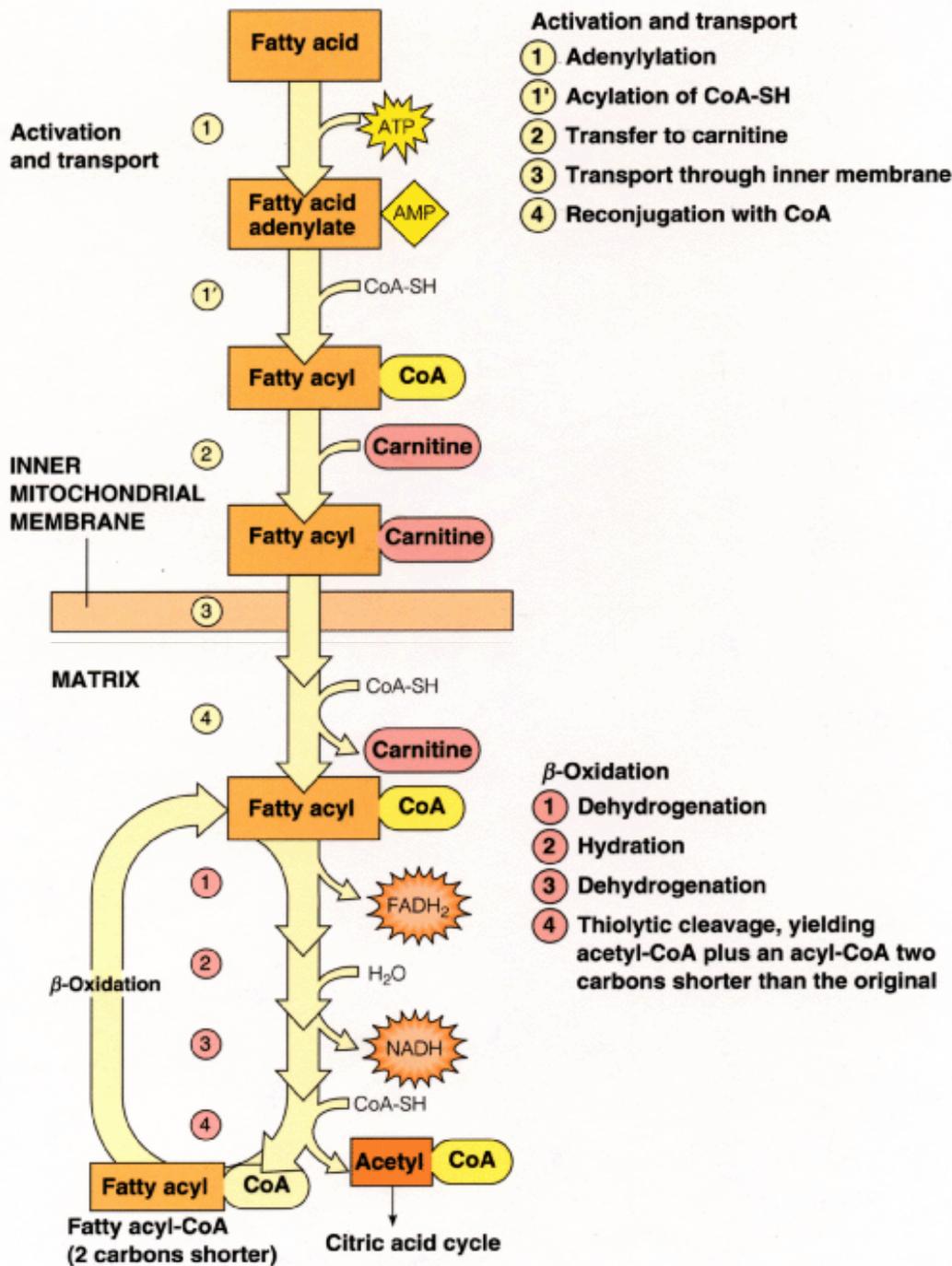
Fatty Acid Oxidation Disorders  
Galactosemia  
Biotinidase Deficiency

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# What are Fatty Acid Oxidation Disorders?

- FAO disorders are autosomal recessive inherited conditions
- Enzymes necessary for fatty acid breakdown have reduced or no activity
- Breakdown, or oxidation, of fatty acids is necessary for energy production when glucose levels are low
- Without this energy supply, individuals may have recurring low blood glucose levels
- Most fatty acid disorders do not surface until a fasting challenge has been encountered sometime after birth

# Mitochondrial Fatty Acid $\beta$ -Oxidation Pathway



# What are Fatty Acid Oxidation Disorders?

- In newborns, a "fasting state" can be produced in as little as four hours without feeding
- Fasting states can also be caused by illnesses such as viral or bacterial infections
- Depending on the disorder, an affected infant could develop symptoms and suffer metabolic crisis anywhere from within 24 hours after birth up to sometime during early childhood when they begin sleeping through the night or switch to solid food
- Affected individuals may have vomiting, lethargy, seizures or coma

# What are Fatty Acid Oxidation Disorders?

- Failure to diagnose fatty acid disorders may result in excessive fat buildup in the liver, heart, muscles and kidneys
- Symptoms can include hepatic failure, encephalopathy, heart and eye complications or problems with muscle function
- Many of these symptoms can lead to death if untreated
- Many deaths due to fatty acid disorders have been misdiagnosed as Sudden Infant Death Syndrome (SIDS) or Reye's Syndrome in the past

# Screening for Fatty Acid Oxidation Disorders

- The fatty acids from the infant's blood are of different carbon chain lengths and are called "acyl" groups.
- They are covalently bound to the endogenous amino acid, carnitine
- The acylcarnitines are abbreviated with a "C" for carbon, followed by the number of carbons in their chain
- Each disorder has its own profile of acylcarnitines that rise in the infant's blood from the result of a disabled or missing enzyme in the fatty acid oxidation pathway

# Newborn Screening for Fatty acid Oxidation Disorders

- Short chain acyl CoA dehydrogenase deficiency (SCAD)
- Medium chain acyl CoA dehydrogenase deficiency (MCAD)
- Very long chain acyl CoA dehydrogenase deficiency (VLCAD)
- Long chain 3-hydroxy acyl CoA dehydrogenase deficiency (LCHAD)

# Newborn Screening for Fatty acid Oxidation Disorders

- Trifunctional protein deficiency (TFP)
- Multiple acyl CoA dehydrogenase deficiency (MADD) (Glutaric aciduria type II)
- Carnitine uptake defect (CUD)
- Carnitine palmitoyl transferase types 1 and 2 (CPT1 and CPT2)
- Carnitine acylcarnitine translocase (CAT)

# Fatty Acid Oxidation Disorders

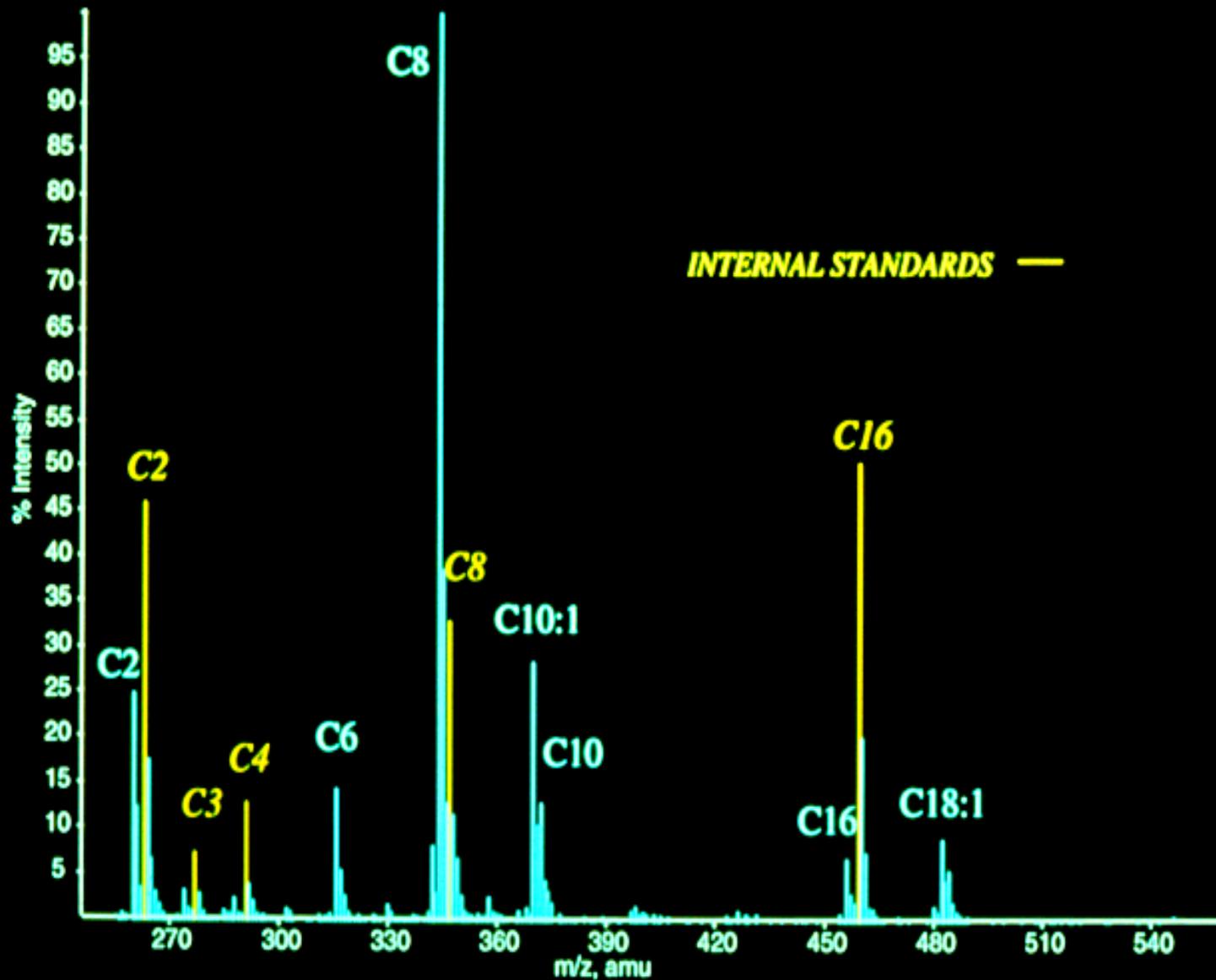
## Clinical Features

- Hypoglycemia
- Hypoketosis
- Acidosis
- Encephalopathy
- Reye-like syndrome with liver dysfunction or failure
- Cardiomyopathy
- Skeletal muscle myopathy
- Eye problems---pigmentary retinopathy
- Sudden Infant Death Syndrome (SIDS)

# Medium chain acyl CoA dehydrogenase (MCAD) deficiency

- Most common of the FAO disorders
- 1 / 6000 to 1 / 12,000 newborns
- Usual presentation is at 1-3 years of age with hypoketotic hypoglycemia, vomiting, dehydration and encephalopathy during intercurrent illness
- May present soon after birth and has been associated with SIDS
- 25% of children die with first presentation
- Many suffer irreversible brain injury
- Treatment is simple avoidance of fasting, lower fat diet and carnitine supplement

# Acylcarnitine Profile from a Filter Paper Blood Spot: MCAD Deficiency



# Child A - MCAD Before Screening

- Healthy until 18 months of age
- Became ill and slept for 20 hours without eating or drinking
- Unarousable and taken to the hospital
- Severe hypoglycemia with brain injury
- Intractable seizures requiring 3 medications
- Spastic quadriplegia
- Profound mental retardation---cannot walk or speak
- G-tube fed

# Child B - MCAD After Screening

- Detected by newborn screening at a few days of age
- Follow-up testing confirmed MCAD deficiency
- Never became ill
- Followed regularly in Genetics Clinic
- Dietary management with avoidance of fasting and carnitine supplement
- Has required an admission to the hospital for IV fluids for a couple of days
- Normal growth and development

# Long Chain Fatty Acid Oxidation Defects (LCHAD, TFP, VLCAD)

- More likely to present with symptoms as a newborn or in early infancy
- Lactic acidosis
- Hypoglycemia
- Cardiomyopathy
- Sudden infant death syndrome
- Retinopathy in LCHAD and TFP deficiency
- Skeletal muscle myopathy / recurrent rhabdomyolysis in older patients

## Multiple Acyl-CoA Dehydrogenase Deficiency (Glutaric Aciduria type 2)

- Enzyme defect results in impairment of many steps in the fatty acid oxidation pathway
- GA2/MADD often presents in the neonate with poor feeding, lethargy, acidosis and facial dysmorphism and kidney anomalies
- Milder forms may present in childhood or later in life
- Laboratory tests reveal hypoketotic hypoglycemia, metabolic acidosis and hyperammonemia

# SCAD Deficiency

- Defect in the short chain acyl-CoA dehydrogenase
- Metabolic acidosis and hypotonia
- Most affected neonates are asymptomatic and the mild forms are most common
- Some risk for hypoglycemia
- A severely affected neonate can be extremely ill with vomiting, lethargy, seizures, and hypoketotic hypoglycemia
- Skeletal muscle myopathy
- Treatment consists primarily of avoidance of fasting and vitamin/cofactor supplementation

# Carnitine Uptake Disorder (Carnitine Transporter Defect)

- Also called primary carnitine deficiency
- CUD is caused by a defect in the carnitine transporter that moves carnitine across the cell membrane
- Reduced carnitine limits acylcarnitine formation and prevents transport of fatty acids into mitochondria, thereby limiting energy production
- Tissues with high energy needs (skeletal and heart muscle) are particularly affected

# Carnitine Uptake Disorder (Carnitine Transporter Defect)

- Decreased total carnitine (CO) in plasma and overexcretion of carnitine in urine
- Newborn's mother should be investigated because cases of maternal CUD have been identified following abnormal newborn screening in their baby
- Carnitine transporter defect has a variable expression and age of onset
- Characteristic manifestations include lethargy, hypotonia, hepatomegaly, and cardiac decompensation due to cardiomyopathy
- Hypoglycemia is typical in acute episodes

# Carnitine Palmitoyltransferase Deficiency, Type I

- Deficiency of CPT1 prevents fatty acid carnitine-acylcarnitine linkage required to transport fatty acids into the mitochondria.
- Plasma acylcarnitines show elevated free carnitine with low or normal long-chain acylcarnitines
- Prevents fatty acid oxidation needed to generate energy
- Newborns may appear asymptomatic but can progress to fasting hypoketotic hypoglycemia, lethargy, hepatomegaly, and seizures, usually precipitated by fasting or acute illness

# Carnitine Palmitoyltransferase Deficiency, Type 2 and CACT Deficiency

- In both the translocase and CPT2 deficiencies, the acylcarnitines cannot be transported into the mitochondria for fatty acid oxidation
- In addition, the neonatal form of CPT2 deficiency is associated with multiple congenital anomalies
- Plasma acylcarnitine analysis reveals increased C16 and/or C18:1

# Carnitine Palmitoyltransferase Deficiency, Type 2 and CACT Deficiency

- In neonatal form of CPT2 deficiency, the neonate is profoundly ill with marked hypoglycemia, metabolic acidosis, cardiac arrhythmias, and facial dysmorphism
- In the later-onset muscular form of CPT2 deficiency, the neonate is asymptomatic but muscle disease develops in the adolescent or adult years.
- Translocase deficiency presents similarly to the neonatal form of CPT2 deficiency

# Galactosemia

- Galactosemia is caused by the lack of a liver enzyme required to digest galactose (milk sugar)
  - Galactose is a breakdown product of lactose, which is most commonly found in milk products
- Incidence is 1 in 45,000 newborns
- Autosomal recessive disease
- Galactose builds up in the cells and becomes toxic
- Can lead to diarrhea, vomiting, dehydration, jaundice, hepatic failure, hypoglycemia, cataracts, mental retardation and death
- Treatment consists of withdrawal of all foods containing lactose and galactose from the diet

# Galactosemia

- Screened by measuring galactose-1-PO4 uridyltransferase (GALT) enzyme activity
- Missouri discontinued measurement of galactose metabolites in January 2005
- This change decreased borderline abnormal test results due to slightly elevated galactose levels
- Will detect all affected babies, some heterozygotes and most Duarte-galactosemia (DG) cases
- Missouri NBS will not detect the rare epimerase & galactokinase deficiency forms of galactosemia

NOTE: Illinois screens by galactose level, and does enzyme assay only if galactose level is high

# Biotinidase Deficiency

- Biotinidase deficiency affects the way the body uses biotin
- Biotin is a vitamin that helps enzymes called carboxylases make certain fats and carbohydrates and break down proteins
- Biotin is essential for proper growth and development
- A person with biotinidase deficiency cannot use the bound biotin in food
- Low levels of biotin may cause seizures, developmental delay, hearing loss and other serious and life threatening illness

# Biotinidase Deficiency

- About 1 in 60,000 newborns
- In 2009, Missouri began testing for biotinidase activity
- Symptoms appear before 2 years of age
  - Feeding problems, diarrhea, vomiting
  - Alopecia and skin problems
  - Seizures, hypotonia, mental retardation
- Treatment with daily biotin permits normal, healthy lifespan in biotinidase deficiency

# Role of Primary Care Provider

- Parent education
  - Preferably discuss NBS prior to birth
  - Informed consent at first screen (often done by a nurse in the hospital)
- Obtain sample
  - 24-48 hours after delivery
- Send sample to the laboratory in timely manner

# Reporting Results

- Normal result
  - Written report sent to submitter of specimen and to healthcare provider
- Abnormal result
  - Newborn Screening Lab will contact infant's healthcare provider
  - If unable to contact provider, will contact family
  - Depending on degree of abnormality (if moderate to high risk), lab will also call one of the four genetics centers in the state

# Special Needs for Children with Metabolic Disorders

- Medical foods and formulas
- Low-protein food products
- Medications
- Metabolic dietitian
  - Patient and family education
  - Dietary management
- Genetics Clinic follow-up visits
  - Laboratory monitoring
  - Growth and development

# Special Needs for Children with Metabolic Disorders

- It is a challenge to provide specialized medical foods & formulas
  - Age limitation of 6 years old in Missouri for insurance coverage for formulas
- Low-protein food products are not paid for by most insurance companies