CLINICAL PRESENTATION
METABOLIC DISEASE

- Nonspecific problems of lethargy, decreased feeding, vomiting.
- These symptoms can progress to seizure/coma.
- Similar symptoms can be seen with many etiologies including congenital heart defects, sepsis.
- *While most of these disorders are tested for on the newborn screen in Illinois, newborn screening is not consistent from state to state so specific questions on newborn screening is not asked on step I.

NEWBORN CRASH

- Usually term infant with well interval (The placenta filters the fetus’s blood prior to birth)
- Non-specific poor feeding, vomiting, lethargy, progressing to seizures and coma.
- Occasionally abnormal odor of urine.
A baby presents at 4 days of life with lethargy and decreased p.o. intake. A septic workup is negative. He is noted to have a blood gas with a pH of 7.49 (nl 7.38-7.42). The NH₃ is 1200 (NL 30-120). What is the most likely diagnosis?

A. Ornithine Transcarbamylase deficiency
B. Maple Syrup Urine Disease
C. MCAD
D. Galactosemia
E. Phenylketonuria (PKU)
**METABOLIC ACIDOSIS**

- Decreased blood pH, caused by the accumulation of H⁺.
- Decreased bicarbonate, as excess HCO₃ and H₂CO₃.
- Decreased PaCO₂ because of compensatory hyperventilation.

**METABOLIC DISORDERS**

- Results from the accumulation of organic anions.
- Clinically there is usually persistent mild metabolic acidosis with intermittent episodes of acute metabolic decomposition.

**Henderson-Hasselbach equation** measures the anion gap.
- Plasma Na⁺ (plasma Cl⁻ + HCO₃⁻)
- (Normal anion gap is 10-15)
METABOLIC ACIDOSIS

- Normal anion gap (hyperchloremia)
- Abnormal losses of $\text{HCO}_3^-$

- Expanded anion gap
- Accumulation of fixed acid

- Diarrhea, RTA
- Organic acidopathy
- Ketoacidosis
- Lactic acidosis

ORGANIC ACIDURIA

- There are many pathways and enzyme defects resulting in the group of Organic acidurias.
- Clinical features usually include decomposition in the first 2 weeks of life.
- Glutaric acidemia often presents later
- Acidosis, elevated anion gap, elevated lactic acid, hypoglycemia.

ORGANIC ACIDURIA'S

- Most present in the first 1-2 weeks of life
  - Methylmalonic
  - Isovaleric
  - Propionic
  - Glutaric acidemia (present in the first 1-2 years of life)
CLINICAL FEATURES OF ORGANIC ACIDEMIAS

- acidosis
- hypoglycemia
- bone marrow suppression
- hyperammonemia (200-600)

AMINO ACIDEMIA

Amino acids are the building blocks of proteins. There are essential amino acids. The remainder are made from each other.

Various enzymatic defects can result in the inability to convert one amino acid to another.

PHENYLKETONURIA (PKU)

- Phenylalanine is converted to tyrosine.
- When the enzyme PAH (phenylalanine hydroxylase) is nonfunctioning PHE is shunted to phenylpyruvate which is then converted to acids.
- These acids are toxic to the brain.
- If untreated infants may loose 50 IQ points in the first year of life.
- Autosomal Recessive inheritance
CLINICAL CHARACTERISTICS/MANAGEMENT OF PKU

- In the US, the majority of babies are picked up by newborn screening.
- If baby is not picked up by presymptomatic screening, presenting symptoms include poor weight gain, microcephaly, “mousy/musty” odor of the baby.

MANAGEMENT FOR PKU

- Low protein diet with limited phenylalanine, just enough PHE for growth.
- Kuvan is a medication with can improve enzyme function in patients with deficient but some enzyme activity.
- Restrict any “diet sodas” with Aspartame. Aspartame contains high levels of amino acids.
- Lifelong treatment is needed.
- Mother with poorly controlled phenylalanine levels can have a baby with multiple birth defects. In most cases the baby does not have PKU but the elevated phenylalanine during the pregnancy is teratogenic.

HOMOCYSTINURIA

- The amino acid Homocysteine is converted to Cysteine by the enzyme Cystathionine synthase.
- When this enzyme is nonfunctional homocysteine is converted to homocystine and excreted in the urine.
- Elevated homocysteine results in a prothrombic state that increases the risk of blood clots.
- Autosomal Recessive inheritance
HOMOCYSTINURIA

Unlike most metabolic disorders, patients with homocystinuria lack dysmorphic features.

- Marfanoid habitus (long fingers, joint hypermobility, tall stature)
- Cognitive delays
- Downward lens dislocation
- Risk of blood clots, this can result in ischemic stroke or pulmonary embolism

CASE 1

- 12 day old infant presents for routine follow after discharge from the nursery. He was born full term without complication to a 32 year old G1P1. All serology were negative.
- Mother states that the baby is having difficulty breastfeeding. She wonders if she should change to formula/bottle feeding. The mother also noticed that he “throws up” often. His urine has a sweat smell.
- The baby has lost 7% of his birth weight.
- Physical Exam unremarkable

CASE CONTINUED

4 days later the baby presents to the ER unresponsive and hypertonic. His eyes are deviated up and he begins to convulse.
LABORATORY VALUES

- Blood Ph 7.34 (nl 7.38-7.42)
- HCO3 15 (nl 20-24)
- NH3 180 (nl 60-80)
- Lactic acid 1.4 (nl 0.5-1.5)
- Glucose 70 (nl 75-95)

MAPLE SYRUP URINE DISEASE

- Baby deteriorates in the first 1-2 weeks of life
- NH3 normal or ↑
- Lactate normal
- Glucose normal/low hypoglycemia
- Maple syrup odor (sweet) in urine (or ear wax)
- Serum amino acid have an elevation of leucine, isoleucine, valine and Alloisoleucine
- In Vermont Maple Syrup
- Inherited in an autosomal recessive fashion
- Incidence 1/100000-1/300000 (1/200 in Mennonites)

Caused by a nonfunctional enzyme in the BCKD complex, which catalyzes the decarboxylation of the alpha-ketoo acids of leucine, isoleucine, and valine to their respective branched-chain acyl-CoAs.

- The elevated isoleucine results in the sweet smell to the urine.
- The elevated leucine is transported to the brain. In the brain leucine is converted to glutamate and glutamine.
- Glutamate and Glutamine results in lethargy and damage to neurons.
- Management: diet low in protein with limiting branch chain amino acids.
The purpose of the urea cycle is to dispose of nitrogen waste and biosynthesis of arginine. When this cycle is not working correctly the NH₃ is elevated. Incidence of urea cycle defects is 1/30,000 with X-linked Ornithine Transcarbamylase deficiency (OTC) being the most common.

- Ornithine Transcarbamylase deficiency (OTC)
- Citrullinemia
- Argininosuccinate lyase deficiency
- Arginase deficiency

<table>
<thead>
<tr>
<th>URINE SMELLS AND METABOLIC DISEASE</th>
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<td>Maple Syrup Urine Disease</td>
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<tr>
<td>Isovaleric Acidemia</td>
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<tr>
<td>Tyrosinemia</td>
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CASE 2

- Baby boy born by repeat C-section. The first day of life his was nursing well. He is 36 hours of life. He now appears hypotonic and lethargic. His blood gas indicates a pH of 7.49 (nl 7.38-7.42) with a HCO3 of 26. Septic workup including CBC and LP are normal.

- NH3 1500 (nl 60-120)

LABS

- PH 7.49
- HCO3 26
- NH3 1500

SYMPTOMS OF A UREA CYCLE DEFECT

- Because of the accumulation of NH3, patients with Urea cycle defects are often ALKALOTIC.
- The NH3 can reach high levels (in the thousands).
DIAGNOSIS

Urea Cycle
The most common cause, especially in a male, is Ornithine Transcarbamylase (OTC).
Serum amino acid analysis and specific enzyme analysis is needed to determine which enzyme is involved.
In OTC, urine organic acids will show elevation of Orotic acid and amino acids will show low Citrulline.

LATE-ONSET PRESENTATION FOR METABOLIC DISORDERS

CASE 4: LATE ONSET: RECURRENT METABOLIC CRISIS

- An 18 month of female has been growing and developing well except for 2 episodes of vomiting and dehydration at 9 and 12 months of age. They were both thought to be caused by viral illness. On admission she is dehydrated and unresponsive except for grimacing for painful stimuli. Her tone is increased and reflexes are hypertonic.
**Laboratory Values**

- pH = 6.99 (nl 7.35-7.40)
- HCO3 = 5 (nl 20-24)
- Lactic Acid = 1.2
- NH3 = 120 (nl 60-80)

**Glutaric Acidemia**

- Megalencephaly
- Often children have normal development until their first episode.
- Some have profuse sweating or unexplained fevers, irritability.

**Diagnosis of Glutaric Acidemia**

- Elevation of glutaric acid in urine organic acids (3-OH glutaric)
- MRI abnormalities including lesions to the basal ganglia and subdural hematomas
- The glutaric acid is toxic to the brain resulting in brain atrophy and additional fluid around the brain resulting in microcephaly-macrocephaly.
- The subdural hematomas are believed to result from inflammation or tearing of vessels
- The most common cause of subdural hematomas in children is ASUAE
A baby presents at 4 days of life with lethargy and decreased p.o. intake. A septic workup is negative. He is noted to have a blood gas with a pH of 7.49 (nl 7.38-7.42). The NH₃ is 1200 (NL 30-120). What is the most likely diagnosis?

A. Ornithine Transcarboxylase deficiency
B. Maple Syrup Urine Disease
C. MCAD
D. Galactosemia
E. Phenylketonuria (PKU)

A 6 month old presents to the ER with lethargy. He was diagnosed with a viral illness 3 days prior. He had poor p.o. intake for the past 2 days. Initial laboratory studies showed glucose of 50 (nl 80-100). Blood gas showed pH 7.38 (nl 7.38-7.42), CO₂ 21, lactic acid was 2.5 (nl .5-1.5), NH₃ was 80 (nl 30-120). The urine dip was negative for ketones. The most likely diagnosis

A. Ornithine Transcarbamylase deficiency
B. Maple Syrup Urine Disease
C. MCAD
D. Galactosemia
E. Phenylketonuria (PKU)

FATTY ACID METABOLISM
MEDIUM-CHAIN ACYL-COENZYME A DEHYDROGENASE DEFICIENCY (MCAD)

- Incidence 1/6,000
- Autosomal Recessive
- Enzyme is involved in mitochondrial fatty acid B-oxidation.
- Symptoms occur after prolonged fasting.
- Hypoketotic hypoglycemia, "Reye like illness"
- Organic acids and acylcarnitine studies show an increased C6-C10 dicarboxylics.
- 2-3% of Sudden Infant Death (SIDS) deaths are a result of MCAD.

FATTY ACID OXIDATION

DISORDERS OF FATTY ACID OXIDATION (FAO)/MASS SPEC

- Very long Chain Fatty acid oxidation disorder (VLCHAD)
- Long Chain Fatty acid oxidation disorder (LCAD)
- Medium Chain Fatty acid oxidation disorder (MCAD)
- Short Chain Fatty acid oxidation disorder (SCAD)
MCAD DEFICIENCY

- Most common of the disorders of fatty acid oxidation
- Not described until 1983
- Treatment: carnitine supplementation, low fat diet, prevent fasting state.

USUAL PRESENTATION

- Episodic illness with hypoglycemia usually occurs first between 3 months and 2 years of age.
- Usually follows fasting for 12 hours or more or with intercurrent infectious disease.
- Acute episode often starts with vomiting, lethargy, or even seizures.
- Can progress to coma rapidly.

LABS

- Hypoglycemia
- Urine dip usually negative for ketones despite fasting state.
- Hyperammonemia, high uric acid, high CPK all indicative of FA oxidation disorder.
A 6 month old presents to the ER with lethargy. He was diagnosed with a viral illness 3 days prior. He had poor oral intake for the past 2 days. Initial laboratory results showed glucose of 50 (nl 80-100). Blood gas showed pH 7.38 (nl 7.38-7.42), CO2 21. The lactic acid was 2.5 (nl .5-1.5), NH3 was 80 (nl 60-120). The urine dip was negative for ketones. The most likely diagnosis

B. Ornithine Transcarbamylase deficiency
C. Maple Syrup Urine Disease
D. MCAD
E. Galactosemia
F. Phenylketonuria (PKU)

A newborn begins vomiting after feeding and is jaundiced. Treatment for possible sepsis is initiated. A blood screen of galactosemia is positive. Which of the following studies would also be expected?

A. Urine amino acids will show an elevation of phenylalanine
B. Urine organic acids indicates elevation of branched chain amino acids
C. Ammonia is elevated
D. Urine is positive for reducing substances
E. Blood culture is positive for growth of Streptococcus
GALACTOSEMIA

- Results from the inability to convert Galactose to Glucose
- Galactosemia usually results from the absence of the enzyme Galactose-1-phosphate uridyl transferase (GALT)
- Two other enzymes in the conversion from Galactose to UDP-Glucose are GALK and GALE
- When Galactose cannot be converted to glucose it is converted to galactitol which is toxic in the liver and brain
- It can accumulate in the lens of the eye resulting in cataracts
- Urine will show reducing substances (unmetabolized sugars)
- Autosomal Recessive Inheritance

CLASSICAL GALACTOSEMIA

Clinical features include:
- Jaundice
- Hepatomegaly
- Vomiting, feeding intolerance
- E. coli sepsis
- Cataracts
- Untreated babies can rapidly progress to hepatic toxicity and death from sepsis or bleeding.

TREATMENT FOR GALACTOSEMIA

- Lactose free diet
- During infancy Soy formula (ISOMIL) instead of Similac or Enfamil.
- Breast milk has lactose!
- This is tested for on the newborn screen
A newborn begins vomiting after feeding and is jaundiced. Treatment for possible sepsis is initiated. A blood screen of galactosemia is positive. Which of the following studies would also be expected?

- A. Urine amino acids will show an elevation of phenylalanine
- B. Urine organic acids indicates elevation of branched chain amino acids
- C. Ammonia is elevated
- D. Urine is positive for reducing substances
- E. Blood culture is positive for Streptococcus

GLYCOGEN STORAGE DISEASES

- Glycogen is another method to store sugars
- A group of inherited diseases characterized by nonfunctional enzymes involved in either break down or synthesis of glycogen.
- Hallmark of the disease is accumulation of abnormal amounts of glycogen in tissues and organs including the liver and skeletal muscle.
- 1/20,000-25,000

A college student comes into clinic. He recently started a weight lifting program. After a 30 minute work out he experiences severe pain which has not improved over the past week. The day prior he had red colored urine. A urine dip is negative for blood. A CK was noted to be elevated at 6000 (nl 30-100). What is the most likely diagnosis?

- A. Becker’s Muscular Dystrophy
- B. MCAD
- C. Galactosemia
- D. Citrullinemia
- E. McArdle’s Disease
GLYCOGEN

Glycogen is a way to store sugars. They are kept in long chains with branches. To use the “saved sugars” we need to free them from this complex of branches.

HEPATIC GROUP

- Type I: Von Gierke Disease
- Type III: Debrancher Defects
- Type IV: Branching Enzyme Defect
- Type VI: Liver Phosphorylase

TYPE I GLUCOSE-6-PHOSPHATASE DEFICIENCY: VON GIERKE

- Clinically present
  - At 3-4 months old
  - Hepatomegaly
  - Failure to thrive
  - Fat cheeks with thin extremities
  - Hypoglycemia with seizures
- Labs
  - Hypoglycemia
  - Lactic acidosis
  - Hyperuricemia
  - Hyperlipidemia
- Treatment
  - Preventing hypoglycemia with continuous feed
  - Replacing Glucose and Fructose in diet
VON GIERKES DISEASE: GLUCOSE-6-PHOSPHATASE DEFICIENCY

- When blood glucose is low, the body breaks down glycogen.
- Glycogen is converted to Glucose-1-Phosphate and then Glucose-6-Phosphate.
- The Glucose-6-Phosphate is then converted to Glucose.
- The enzyme Glucose-6-Phosphatase does not function in patients with Von Gierkes.
- As a result, the excess Glucose-6-P is converted to pyruvate.
- Elevated pyruvate causes lactic acidosis and hyperuricemia in the Citric acid cycle.

TYPE III DEBRANCHER DEFICIENCY CORI DISEASE

- Deficiency of glycogen debranching enzymes.
- When the enzyme responsible for this process is not present, abnormal glycogen is formed.
- Symptoms include:
  - Hepatomegaly
  - Hypoglycemia
  - Short stature
  - Skeletal myopathy
  - Cardiomyopathy

MUSCLE GLYCOGEN STORAGE DISORDERS

- Type II: Pompe Disease
- Type V: McArdle
- Type VII: Phosphofructokinase deficiency
TYPE V MCARDLE

- Deficiency of the enzyme muscle phosphorylase.
- PYGM gene codes for this enzyme.
- It is inherited in an autosomal recessive fashion.
- Absence of the enzyme results in reduced ATP generation by glycogenolysis.
- Symptoms usually begin in the early 20's.
- Exercise induced muscle cramps and exercise intolerance.
- Burgundy colored urine.
- Diagnosis: muscle biopsy identifying glycogen in muscle OR PYGM gene test (100% of patients have a mutation).
- Treatment: avoid strenuous exercise, IVF with glucose during times of Rhabdomyolysis.

TYPE VII PHOSPHOFRUCTOKINASE DEFICIENCY

- Lack of the enzyme Fructose-6-phosphatase.
- Symptoms similar to McArdle, including early onset of fatigue and pain.
- Differences from McArdle:
  - Presents in childhood.
  - Hemolysis occurs.
  - Increases uric acid levels.
  - Exercise intolerance is much worse after carbohydrate meal.

A college student comes into clinic. He recently started a weightlifting program. After a 30 minute work out he experiences severe pain which has not improved over the past week. The day prior he had red colored urine. A urine dip is negative for blood. A CK was noted to be elevated at 6000 (nl 30-100). What is the most likely diagnosis?

A. Becker's Muscular Dystrophy
B. MCAD
C. Galactosemia
D. Citrullinemia
E. McArdle's Disease
CONCLUSION

• Try to put metabolic disorders into categories.
• Try to categorize them by most common differentiating features (e.g., maple syrup/sweet smell in urine, glutaric acidemia/subdural hematomas, family history of SIDS/MCAD).
• Most newborn inborn errors of metabolism, including all organic acidemias, are tested by newborn screening in Illinois.

USMLE LIKE QUESTION

A 24-year-old woman with phenylketonuria (PKU) has her first child. Although there is no family history of PKU in the father's family, the baby is born with microcephaly and the level of phenylalanine at birth is elevated. What is the most likely cause for the baby's microcephaly?

A. The baby has PKU
B. The baby is a carrier of a mutant enzyme for phenylalanine hydroxylase
C. The father has PKU
D. Phenylalanine was not adequately restricted in the mother during the pregnancy

USMLE LIKE QUESTION

The condition from the pedigree has a prevalence in the population of 1/40,000. What is the chance the affected individual indicated by the arrow will have an affected daughter?

A. 1/40,000
B. 1/200
C. 1/100
D. ¼
E. ½
A 9-year-old female has mild mental retardation. She was healthy at birth. She presented in the first week of life with vomiting, lethargy and seizures. An amino acid screen identified elevation of leucine, isoleucine and valine. The baby was placed on a special diet. She has had no medical complications since that time. Which of the following enzymes is most likely deficient in this child?

A. Branched chain ketoacid dehydrogenase
B. Cystathionine synthetase
C. Methylmalonyl CoA mutase
D. Ornithine transcarbamoylase
E. Propionyl CoA carboxylase

A 2-month-old child is evaluated for failure to thrive. During the examination, the child has a seizure. On serum chemistries, severe hypoglycemia, hyperlipidemia, lactic acidosis, and ketosis. Physical examination is remarkable for hepatomegaly, a finding confirmed by CT scan. Which of the following diseases best accounts for this presentation?

A. Gaucher
B. McArdle disease
C. Nieman-Pick disease
D. Pompe disease
E. Von Gierke