Inborn Errors of Metabolism

Usual presentation of inborn error of metabolism

- Healthy at birth .
- Decomposition occurring within days or weeks of birth.

Signs and Symptoms of Metabolic Disease

- Failure to thrive (weight below the 5%)
- Encephalopathy
- Seizures
- Hypotonia
- Diarrhea
- Vomiting
- Hepatomegaly

Healthy at Birth

- Baby with APGARs or 9/9
- Nonspecific problems of lethargy, decreased feeding, vomiting.
- These symptoms progresses to seizure/coma.
- Such a pattern can be seen with many etiologies including congenital heart defects, sepsis, but is a sign of an inborn error of metabolism.

Newborn Crash

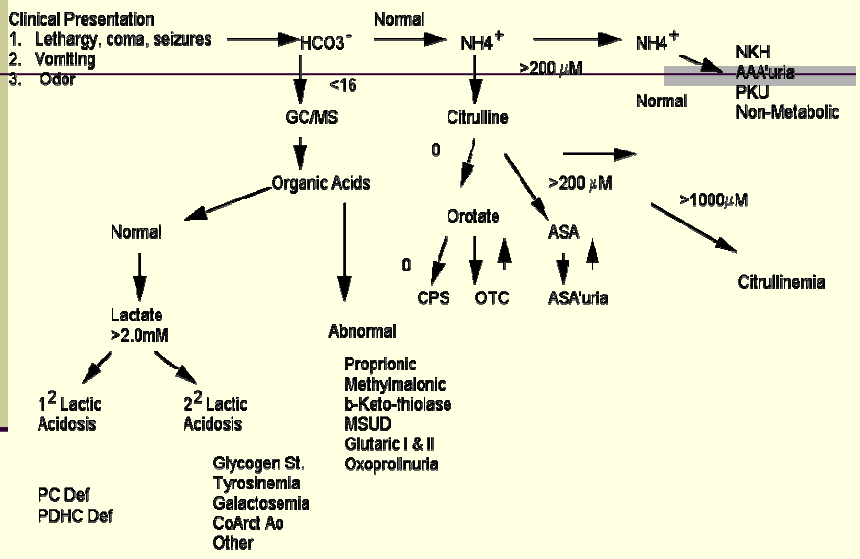
- Usually term infant with well interval (The placenta filters the fetuses blood prior to birth)
- non-specific poor feeding, vomiting lethargy, progressing to seizures and coma
- occasionally abnormal odor of urine.

Clinical Characteristic

- Abnormal odors of urine
- Abnormal skin or hair findings
- Menkes: kinky, steely hair
- Biotin disorders: alopecia, rash
- non-ketotic hyperglycinemia: hiccups

Differential Diagnosis of newborn crash

- **Adrenal insufficiency, sepsis, congenital heart disease, asphyxia**
- Amino acid abnormality (MSUD)
- Urea cycle abnormality
- Organic aciduria (proprionic, methylmalonic)
- Congenital lactic acidosis
- Mitochondrial disorder



Metabolic Acidosis

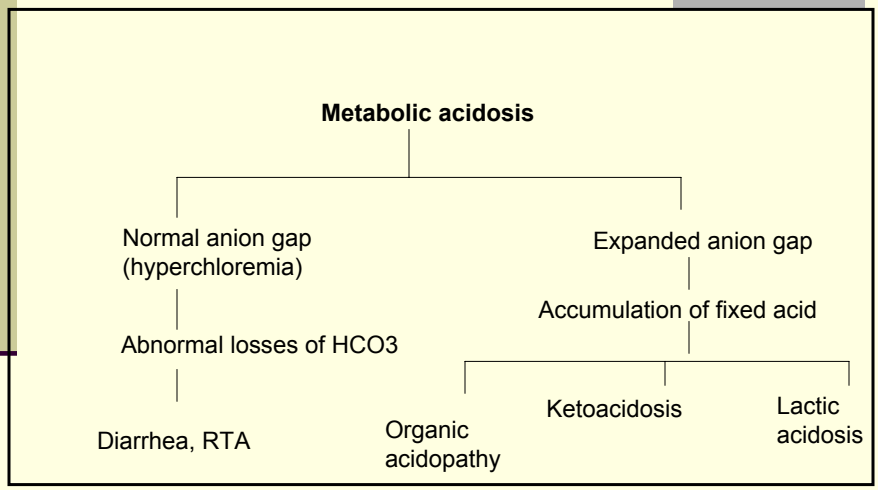
- Deceased blood pH, caused by the accumulation of H+.
- Decreased bicarbonate, as excess HCO3 and H2CO3.
- Decreased PaCO2 because of compensatory hyperventilation.

- Is the metabolic acidosis the result of abnormal losses of bicarbonate (diarrhea) or accumulation of acid.
- Henderson-Hasselbach equation measures the anion gap.
- Plasma Na- (plasma Cl + HCO3)
- Normal anion gap is 10-15

Metabolic Disorders

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

Metabolic Acidosis



Organic Aciduria

- There are many defects resulting in the group of Organic acidurias.
- Clinical features usually include decomposition in the first 2 weeks of life.
- It can present later with partial enzyme blocks.
- Acidosis, anion gap, elevated lactic acid, hypoglycemia

Organic Acidemias

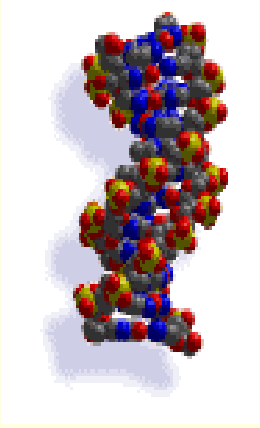
- Methylmalonic
- Isovaleric
- Proprionic
- Glutaric acidemia

Features of Organic acidemias

- Metabolic acidosis
- Hypoglycemia
- Urinary ketones
- Mild elevation of NH3
- Low plasma carnitine
- Elevation of glycine on serum amino acids

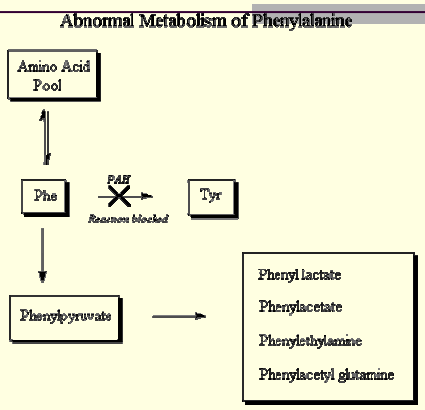
Amino Acidemia

- Amino acids are the building blocks of DNA.
- 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.



Amino Acidemias

- PKU
- Maple Syrup urine disease

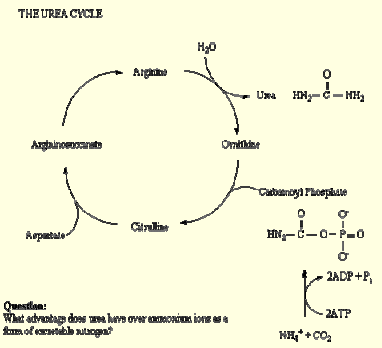


Urea Cycle Defect

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

Urea cycle disorder

- The purpose of the urea cycle is to dispose of nitrogen waste and biosynthesis of arganine
- Incidence 1/30,000 newborns with X-linked OTC deficiency being the most common



Urea cycle disorder

- OTC deficiency
- Citrullinemia
- Argininosuccinate lyase deficiency
- Arginase deficiency

Features of Urea cycle defects

- VERY elevated NH3 (can be in the thousands)
- Normal plasma glucose
- Alkalosis
- Normal plasma lactate
- Normal urine organic acids

Decompensation in **first day of life**

- This is often a sign that things were not going well during the pregnancy.
- Symptoms could represent a bleed or anoxic event prior to delivery.
- Symptoms could represent an inborn error of metabolism the placenta was unable to adequately filter.

Case 1

3 day old infant presents to the PMD for routine follow after discharge from the nursery. He was born full term NSVD without complication to a 32 year old G1P1. All serology were negative. Group B step status of the mother is unknown.

Mother states that the baby is having difficulty breastfeeding. She should change to formula/bottle feeding. Mother also notices that he “throws up” often. The baby has lost 7% of his birth weight.

Physical Exam unremarkable

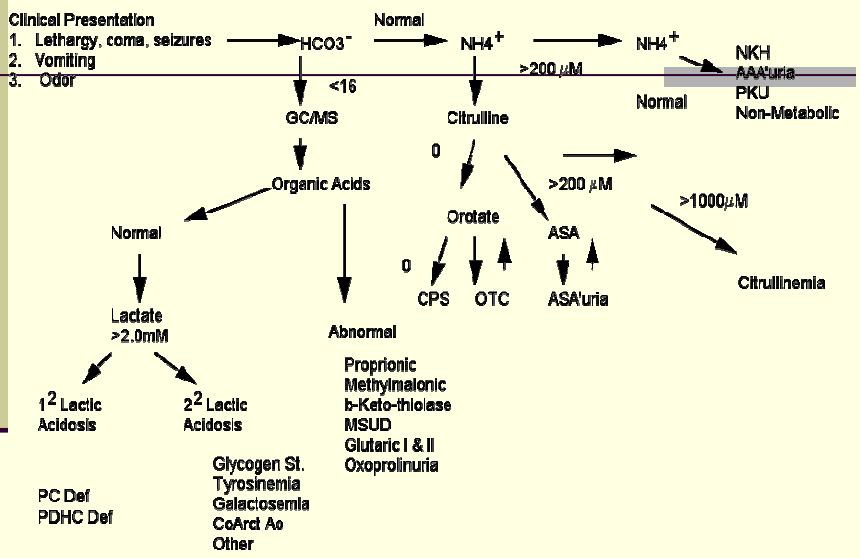
Case Continued

4 days later the baby presents to the ER unresponsive, hypertonic in an opisthotonic position. His eyes are deviated up and he begins to convulse.

Differential Diagnosis?

Laboratory values

- NH3 180 (nl 60-80)
- Lactic acid 1.4 (nl 0.5-1.5)
- Glucose 70 (nl 75-100)
- Blood Ph 7.34
- CO2 19 (nl 20-24)



Maple Syrup Urine Disease

- Baby deteriorates in the first 1-2 weeks of life
- NH3 normal or ↑
- Lactate normal
- glucose normal
- Maple syrup odor to urine (or ear wax)
- Incidence 1/100000-1/300000(1/200 in Mennonites)

Urine Smells and Metabolic disease

Maple Syrup Urine Disease	Maple Syrup
Isovaleric Acidemia	Sweaty Feet
Tyrosinemia	Rotten Cabbage

Maple Syrup Urine Disease: Diagnosis

- Serum Amino Acids
  - Increased leucine, isoleucine, valine, alloisoleucine
  - Decreased alanine (responsible for hypoglycemia)
- Urine Amino Acids
  - Increased leucine, isoleucine, valine
  - Increased ketoacids of leucine, isoleucine, valine

Case 2

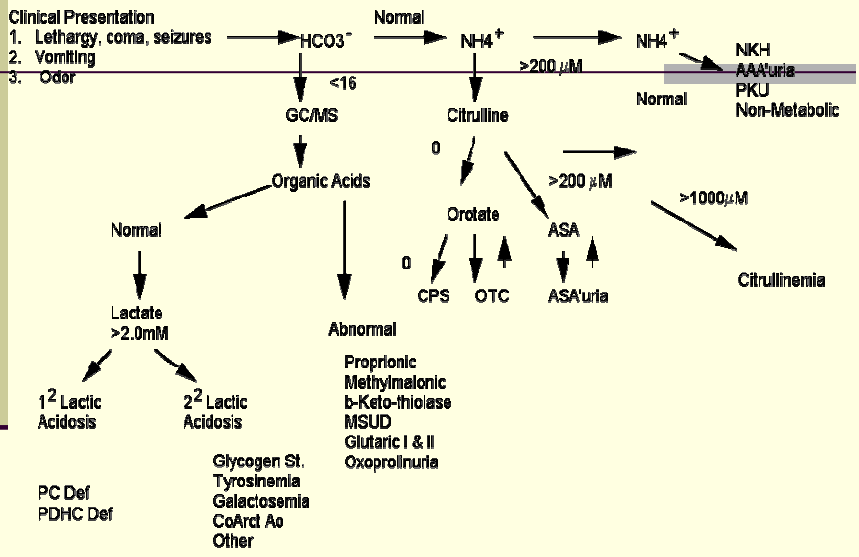
- A 5 day old presents to ER with 3 day history of poor feeding and vomiting. Over the past 24 hours has been lethargic, limp and breathing rapidly.
- The pregnancy, labor and delivery were unremarkable. He was discharge home a 2 days of age.

Physical Exam

- On exam the baby appeared 5% dehydrated, poorly responsive. He was pale with perioral cyanosis. His heart rate was 170/min and respiratory rate was 60/min. His blood pressure was low. His liver is enlarged. He was noted to be hypotonic with decreased reflexes.

Laboratory values

- pH=7.15 (nl 7.35-7.40)
- pCO2=18
- HCO3=7 (nl 20-24)
- Glucose 50 (nl 80-100)
- WBC 2.1
- NH3=240 (nl 60-80)
- Urine with 3+ ketonuria



Differential Diagnosis

- *Organic acidemia*
- Aminoacidemia
- Urea cycle disorder

Organic Acidemias

- Methylmalonic
- Isovaleric
- Proprionic

What to send next

- Serum amino acids
- Urine organic acids

How do you treat the baby prior to the Laboratory confirmation?

Next step

- Maximize glucose, hydrate, remove protein from the diet.
- Send urine organic and serum amino acids
- Do not feed until results are obtained!

Clinical Features of Organic Acidemias

- Ketoacidosis
- elevated glycine on serum amino acids
- hypoglycemia
- bone marrow suppression
- hyperammonemia (200-600)

Case 3

- Baby boy born by repeat C-section. His APGARS were 9 and 9. The first day of life his was nursing well. He is 36 hours of life. He now appears hypotonic and lethargic. He has hypothermia. His blood gas indicates a ph of 7.49 with a CO2 of 26. Septic workup including CBC and LP are normal.

Additional lab values

- NH3 1500

Differential Diagnosis

Next Step

- Remove all protein from the diet
- Maximize glucose
- Consider hemodialysis to lower Ammonia

Intermittent Late-onset presentation

Intermittent Late-onset presentation

- 1/3 of patients with inborn errors of metabolism have an onset after age 1.
- Recurrent attacks of coma, recurrent vomiting with lethargy and ataxia or **loss of intellectual skills.**

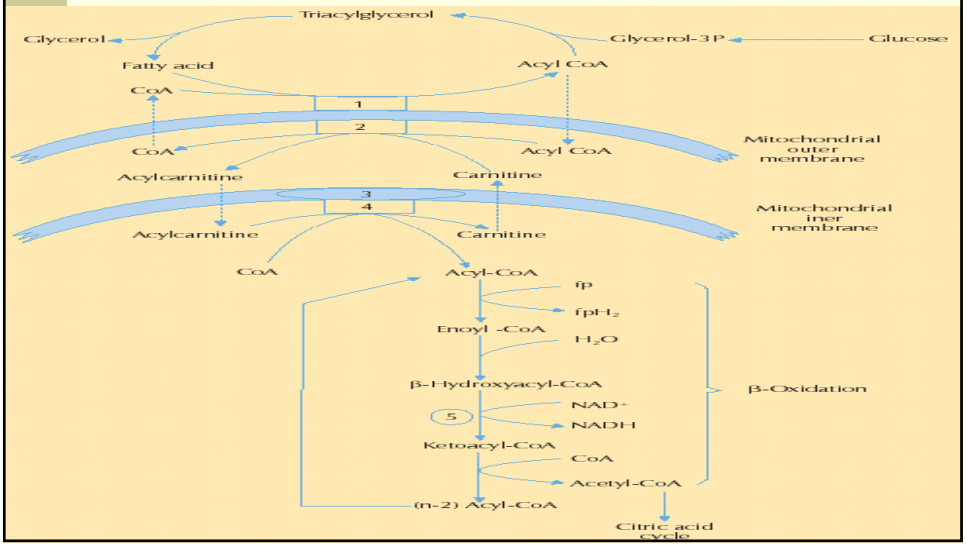
Additional DDx for late onset

- Medium chain acyl CoA dehydrogenase deficiency (MCAD)
- Glutaric aciduria
- Canavan disease

MCAD

- Incidence 1/10,000
- hypoketotic hypoglycinemia, Reye like illness
- organic acids and acylcarnitine studies show an increased C6-C10 dicarboxylics.
- treat with carnitine supplementation, low fat diet
- 2-3% of SIDS deaths are a result of MCAD.

Fatty acid Oxidation



MCAD Deficiency

- Classic disorder of fatty acid oxidation.
- Most common of the FA oxidation disorders (SCAD, LCAD, VLCAD).
- Estimated to occur in every 1 in 6000-10,000 Caucasian births.
- Not described until 1983

Usual Presentation

- Episodic illness usually occurs first between 3 months and 2 years.
- Reye-like episode
- 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.

Major phenotypic expression

- Hypoketotic
- Hypoglycemic
- Myopathy
- Cardiomyopathy
- SIDS
- Hyperammonemia
- Hyperuricemia
- Elevated CPK
- Dicarboxylic aciduria
- Elevated octanoyl- and hexanoyl carnitine
- Deficient activity of medium-chain acyl CoA dehydrogenase

Physical Exam

- Normal
- Lethargic
- Hepatomegaly

Labs

- Hypoglycemic
- Urine dip usually negative for ketones despite fasting state.
- Both can be normal early on.
- Hyperammonemia, high uric acid, high CPK all indicative of FA oxidation disorder.
- Key: *dicarboxylic acids in the urine*.

Case 4
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 hyperactive

Laboratory values

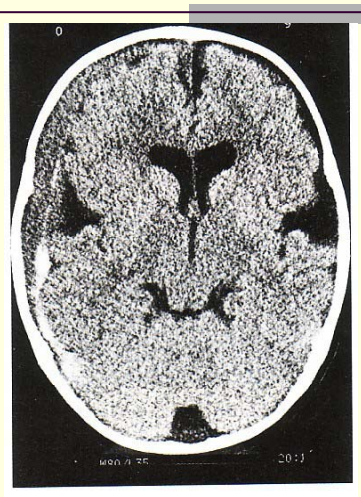
- pH=6.99 (nl 7.35-7.40)
- pCO2=22 (nl 20-24)
- HCO3<5 (nl 20-24)
- NH3=120 (nl 60-80)
- significant ketones in the urine

Glutaric Acidemia

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

Diagnosis of Glutaric Acidemia

- Elevation of Glutaric acid in in urine organic acids
- Low serum carnitine
- MRI abnormalities including lesions to the basal ganglia and subdural hematomas



Treatment for Glutaric Acidemia

- Diet low in tryptophan and lysine
- Riboflavin (coenzyme of dehydrogenase)
- Carnitine supplementation
- Prompt treatment of episodes of vomiting with fluids and glucose.

Case 5

- An 8 day old male presents to the office. The mother noted increased irritability and decreased activity. The family had been to the ER 1 day prior for congestion. The parents were concerned that he hadn't opened his eyes in 2 days and had a poor appetite. He also had an unusual smell in the diaper.

Family history

- This is the first child for these parents. The mother has a 9 year old daughter from a previous relationship. She is healthy.

Which of the following tests would you like to order?

- A. Plasma amino acids
- B. Urine organic acids
- C. Chromosomes
- D. A & B

What additional questions would you ask the parents about the urine smell?

- A. Was is a “mousy” odor
- B. Did the urine have a “sweet” odor
- C. Have you noticed any odors in the ear was?
- D. All of the above

- The newborn screen came back positive for neonatal Maple syrup urine disease.

Elevations in which amino acid is path gnomonic for this disorder?

- A. Leucine
- B. Isolecine
- C. Valine
- D. Allo-isoleucine

Case 6

- A 10 month old presents with the following history, seizures, lethargy, vomiting, metabolic acidosis, hypoglycemia, hyperammonemia, hepatomegaly, and coma.
- PMH: Healthy child until 1 week ago. She developed a febrile illness. She fed poorly for 3 feedings. She then became lethargic and vomited several times.
- In the emergency room she had a seizure. Initial laboratory evaluation revealed hypoglycemia with an elevated ammonia (120).

Case 6 continued

- The family history indicates the child's sister died at 2 years age after a similar viral illness. She was found in the morning unresponsive. The baby was unable to be resuscitated. At autopsy the cause of death was diagnosed as sudden infant death syndrome SIDS.

Which of the following tests would you order to obtain more information?

- A. Plasma carnitine concentration
- B. Urine organic acids
- C. Acylcarnitine profile
- D. Mitochondrial Ox Phos Enzymes
- E. Plasma amino acids

What is the most likely diagnosis?

- A. Influenza respiratory infection
- B. MCAD
- C. Urea cycle disorders
- D. Reye syndrome
- E. Methylmalonic aciduria

What should you do next

- A. Continue IV fluids with 10% dextrose.
- B. Reassure parents that this is a benign condition and should resolve.
- C. Start TPN with intralipids
- D. Withhold all protein feeds

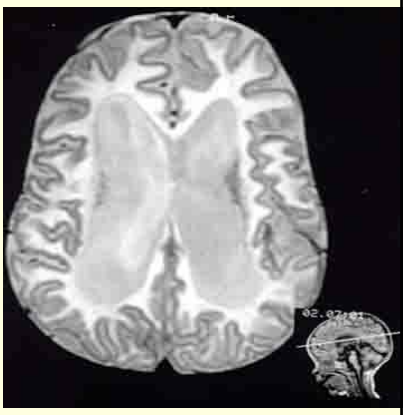
Metabolic Abnormality with Leukodystrophy

Canavans Disease

- Normal at birth
- Between the **2-4 months** begin showing hypotonia, macrocephaly.
- Spontaneous movements decrease.
- Delayed milestones

Canavan Disease

- Milestones achieved such as smiling, grasping are lost.
- Seizures usually occur by the second year.
- Blindness and optic atrophy occur.
- MRI shows extensive loss of myelin.



Genetics of Canavan Disease

- Autosomal Recessive
- increase in N-acetyl aspartic acid in urine, blood, CSF due to an abnormal aspartoacylase gene.
- 2 DNA mutations account for 96% of mutations in the Ashkenazi Jewish population.
- Prenatal testing is possible.

Decompensation with Dysmorphic Features

- Chromosomal abnormality
- Zellweger syndrome
- I-Cell Disease
- Smith-Lemli-Opitz syndrome
- Hydrops fetalis

Chromosomal Aneuploidies

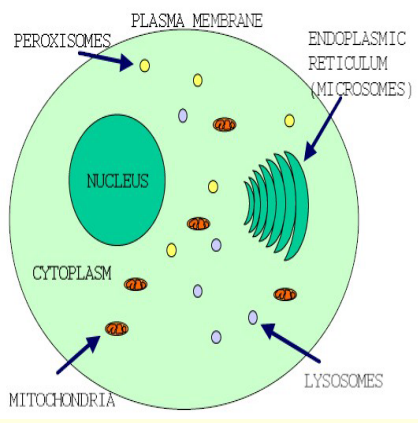
- A dysmorphic child with hypotonia, seizures can result from a variety of chromosomal aneuploidies.
- The most common being trisomy 13 or 18
- However any deletion or rearrangement can result in a similar picture.

Zellweger Syndrome

- Clinical characteristics include dysmorphic facies, hypotonia, seizures (often in the first 24 hours), stippled epephysis
- death usually by 6-12 years
- No peroxisomes seen on biopsies with EM
- elevation on VLCFA

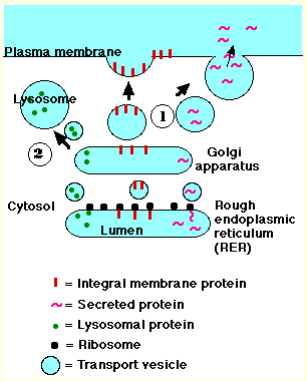
Peroxisomal disorders

- Peroxisomes are cytoplasmic organelles in all mammalian cells
- they contain no nucleic acid
- they are necessary for degradation of very long chain fatty acids
- they synthesize *plasmologens* important in heart and brain



I-Cell Disease

- I-cell disease is a lysosomal storage disease characterized by presentation in the first few months of life.
- It results in the inability of the lysosomes to uptake the a variety of enzymes.
- As a result all of the lysosomal enzymes are elevated.



Variability

- Both types II and III are caused by the same abnormality. In type II there is a complete absence of the enzyme while in type III there is a deficiency.
- The differential is based on clinical features.
- Most patients with type III do not present until later in life.

I-Cell Disease

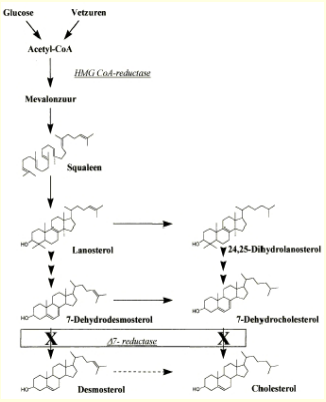
- Clinical features include retardation of linear growth, course facial features early, gibbus deformity by age 6 months, claw hand deformity, thick smooth skin
- Nasal discharge is usually present.

Bone changes in I-cell disease

- Radiologic features are progressive.
- The hands indicate thick and short metacarpals
- The long bones show thickness with poor remodeling.

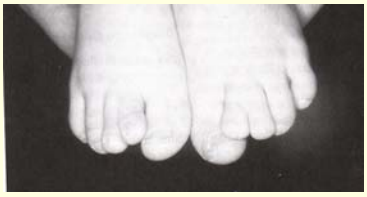
Smith-Lemli-Opitz syndrome

- Caused by a defect of the enzyme 3-beta-hydroxysterol-delta-7-reductase.
- This results in an elevation of 7-dihydrocholesterol



Clinical features of SLO

- Affected individual have low serum cholesterol, dysmorphic features including 2,3 syndactyly of the toes, microcephaly, ptosis of eyelids, postaxial polydactyly, hypospadias, cleft palate and congenital heart defects.



Hydrops Fetalis

- This usually results from a accumulation of fluid in the tissue
- **Immune hydrops** is caused by the destruction of RBCs from an autoimmune process. This can have many causing including RH, ABO incompatibility.
- The loss of blood results in the the edema.
- **Nonimmune hydrops** is the event occurring with no sign of an immune reaction
- Nonimmune hydops has many causes

Causes on Non-Immune Hydrops

- Chromosomal Aneuploidy
- Metabolic abnormality

Nonimmune Hydrops Fetalis

- No evidence of blood group incompatibility
- Incidence – 1 in 1500 to 4000
- Perinatal mortality rate – 52% - 98%
- Etiology varies
  - Southeast Asia – α-thalassemia
  - Caucasian – Cardiac, infectious, chromosomal causes

Chromosomal Abnormalities

- 7 – 45% of hydrops have abnormal chromosomes, more likely if seen before 24 weeks gestation
- Most Common 45,X
- Others
  - Trisomy 21
  - Trisomy 18
  - Trisomy 13
  - Triploidy

Lysosomal Storage Diseases Associated with Hydrops Fetalis

- GM1 gangliosidosis
- Gaucher disease
- Niemann-Pick disease
- Hurler syndrome
- Glycogen storage disease
- Morquio syndrome type A

Conclusion

- Metabolic disorders can present at birth, shortly after or at any time in life.
- Some metabolic disorders are associated with dysmorphic features of the infant/child.
- **Most** metabolic disorders have no dysmorphic features associated.