Good Morning!

OCTOBER 2, 2014
Disorders of Amino Acid Metabolism
What’s my disorder?  PKU

- My disorder is AR
- AKA Følling’s disease
- I Appeared normal at birth…
- But now I have an eczematoid rash and “wolf-like” odor
- I will probably look like these kids→
- My defect is in PAH
A note on PKU:

- Most NBSs are false positives!
  - If positive, order serum amino acids
  - Likely transient!
  - 1-3% are tetrahydrobiopterin (BH4) deficiency
- Initiate diet by 3 weeks of life
  - Damage is irreversible by 8 weeks!
- Maternal PKU
  - Teratogenic effects of elevated levels in untreated mom
  - May result in growth deficiency, microcephaly, mental retardation, congenital heart defects (similar to FAS)
- Hyperphenylalaninemia
  - No clinical manifestations until phenylalanine >20
What’s my disorder?

- My disorder is AR
- I presented with FTT and hepatomegaly with hepatoblastoma*
- X-rays of my bones make it seem like I have rickets*
- I may have RTA* resembling Fanconi syndrome
- My disorder is due to deficiency of fumarylacetoacetate hydroxylase (the final metabolic step)
  - So I have an accumulation of succinylacetone (the cause of my sxs*)
- Treat with NTBC → secondary symptoms develop
- Diet low in tyrosine AND phenylalanine
- Typically have normal intelligence

Tyrosinemia
What’s my disorder?

My disorder is

If you look at my urine, you will see:

1. Fresh urine is normal
2. As it sits and alkalinizes $\rightarrow$ becomes dark brown/black*

Pigmented deposition in ears and sclerae (ochronosis)

Deficiency in homogentisic acid dioxygenase

*3rd step in tyrosine metabolism

Tyrosine levels not increased

Normal intelligence

Alkaptonuria
What is my disorder?

- My disorder is AR
- CNS disease is present in early infancy
  - Symptomatic by 3-5 days of life
  - Feeding difficulties, irregular respirations*, loss of Moro reflex*
  - Seizures, opisthotonos, rigidity (Increased tone)
  - Milder forms: intermittent, with ataxia and repeated episodes of lethargy
- Alloisoleucine* is diagnostic
  - Will have elevations of branched chain amino acids in urine
- Defect is in oxidative decarboxylation of ketoacids
  - Makes urine smell sweet*
What’s my disorder?

Glutaric Aciduria (Type 1)

1. It is a defect in the catabolic pathway of lysine, hydroxylysine, and tryptophan
   - Treat with L-carnitine, riboflavin, and special diet
   - Give me glucose when I’m ill!

2. My disorder may be confused with abuse because I have SDH and retinal hemorrhages*

3. CT/MRI of my brain showed frontal and cortical atrophy at birth....
   - Now, because I got sick, it shows degeneration of caudate nucleus and putamen

4. I used to have macrocephaly but was normal until I got sick...
   - Now I am hypotonic and dystonic*

Glutaric Aciduria (Type 1)
What is my disorder?

Homocystinuria

- My disorder is AR
- I have an increased risk thromboembolism (PE)
  - But my clotting studies normal
- My lens dislocation is downward and medial*
- Some people think I have Marfan’s
  - But I have developmental delay and MR*
  - And my joints are limited* in mobility
- Diagnosed by ↑ urine homocysteine
- Treatment: B6?
What's my disorder?
Nonketotic hyperglycinemia

- My disorder is AR
- Intractable seizures in neonatal period
- In utero I had the hiccups*
- I have large amounts of glycine in body fluids without detectable accumulation of organic acids
  - Highest levels are in CNS
  - Severe MR
- Sodium benzoate seems to reduce CSF glycine levels
Urea Cycle Disorders

Hyperammonemia without acidosis
Ketonuria does not occur!!
What’s my disorder?

Ornithine transcarbamylase deficiency

4. I have the most common Urea Cycle defect (and it is XLR)
   - ↑ CSF glutamine is toxic to my brain!
3. I was normal at birth, but at 5 days of life…
   - I had an ↑ ammonia (level >1000*), lethargy, hypotonia, vomiting, and poor feeding
2. A blood gas showed respiratory alkalosis*
   - I had no liver dysfunction or ketoacidosis
1. The more proximal the defect, the more severe the symptoms
   - I have absent citrulline* and arginine levels
   - Females may present during pregnancy and childbirth
   - OAs establish the specific defect
   - Valproate and haloperidol can “unmask” urea cycle defects*
Organic Acidemias

Often have a “drunk-like” intoxicated picture
A buildup of acids leads to AG Metabolic Acidosis
Look for elevated serum NH4 and ketonuria
Let’s go to the books:

- **Isovaleric Acidemia**
  - Infant with encephalopathy
  - Smell like “sweaty feet”*
  - Precipitated by infection or ↑ protein intake
  - Long term tx: protein restriction

- **Methylmalonic Acidemia**
  - ↑ NH4, ketoacidosis, thrombocytopenia
  - Tx with protein restriction
  - B12 if homocystinuria present too
  - Late onset complications: renal failure and cardiomyopathy
Let’s go to the books:

- **Propionic acidemia**
  - Early: severe ketoacidosis + ↑ NH4, encephalopathy, vomiting, bone marrow depression
  - Late complication: cardiomyopathy
  - Urine: ↑ quantities of 3-hydroxypropionic acids
  - Tx with protein restriction

- **Multiple carboxylase deficiency**
  - Cannot incorporate biotin into carboxylases
  - Triad of alopecia, skin rash, encephalopathy*
  - Can be picked up on NBS for biotinidase deficiency
  - Treat with biotin! (all disease manifestations are reversible)
Disorders of Fatty Acid Oxidation

Autosomal Recessive
Watch for preceding benign illness, during which po ↓
Absence of reducing substances and ketones in urine
What’s my disorder?  
Primary Carnitine Deficiency

- My defect is in the mitochondria and is AR
- It typically presents 3mths – 2yrs:
  - Cardiomyopathy
  - Recurrent episodes of encephalopathy
  - Hypoketotic hypoglycemia*
- Triggered by fasting or common URIs/GI illness

2
- Myopathy of cardiac and skeletal muscle
  - I have the most common heritable metabolic etiology for rhabdomyolysis*

1
- Treat acute presentation with IV 10% dextrose
- Long term: Avoid hypoglycemia! Give L-carnitine
What’s my disorder?

MCAD deficiency

1. Liver biopsy: microvesicular steatosis*
2. Increased C8 and C10 esters
3. Acutely: Increased liver transaminases, CPK and ↓glucose
4. I have the most common disorder affecting mitochondrial fatty acid oxidation and ketogenesis
   Presents in 1st 2 years with fasting induced lethargy and hypoglycemia
   Has been implicated in some SIDS cases*
   Acutely: Increased liver transaminases, CPK and ↓glucose
   Liver biopsy: microvesicular steatosis*
   Increased C8 and C10 esters
   Acute tx: IV glucose and bicarb
   Do you replace MCAD?*
     NO!! The enzyme is missing, not the MCAD
   NBS detects MCAD defic
     Prior to NBS, 25% infants died with first metabolic illness
Disorders of Carbohydrate Metabolism

Glycogen Storage Diseases
What’s my disorder?
Type 1 GSD- von Gierke Disease

- AKA hepatonephromegaly
- My disorder appeared when I was about 3-4 months old*
- I developed hepatomegaly, FTT, hypoglycemia + seizures
- I have a cherub face with thin extremities and short stature, and a big belly*
- Lactic acid, uric acid, triglycerides and cholesterol ALL ↑*
- My liver transaminases are normal!
- If you give me glucagon or epinephrine- my glucose will not increase but lactate will
- I have a defect in glucose 6 phosphatase (the final step)
- I required continuous glucose until 2 yrs, and now I get frequent “doses” of cornstarch
What's my disorder?

McArdle's

5. My disorder is due to decreased ATP production*, resulting in glycogen accumulation,

4. I have exercise induced muscle cramps, but I can find my 2\textsuperscript{nd} wind

3. CPK increased at rest*
   - 50% have burgundy color urine after exercise
   - Ammonia and uric acid increased with exercise

2. Dx is suggested by finding increased ammonia but normal lactate

1. It is a deficiency of phosphorylase
What’s my disorder?

Pompe Disease (GSD II) aka Acid Maltase Deficiency

3.
- Actually a lysosomal storage disorder
- Excess glycogen in lysosomes instead of cytoplasm
  - Defect in glucosidase, which normally breaks down glycogen in lysosomal vacuoles

2.
- Biopsy- vacuoles full of glycogen on staining

1.
- Infantile is most severe (death before 1 year of age)
  - Normal at birth…progressing to FTT and floppiness (aka hypotonia) with muscle weakness*
  - Macroglossia, hepatomegaly and cardiomegaly with CHF common
**What is my disorder?**

**Galactosemia**

- Duarte variant is most common
- I was ok at birth, but then I had my first breast feeding* lesson with mom and...
- I became irritable and hypoglycemic with jaundice and HSM (pretty non-specific, eh?)
- I have cataracts*
- Cannot metabolize galactose-1-phosphate → accumulates in kidney, liver, and brain
- I was also sick with E coli sepsis*
- Suspect if non-glucose reducing substances in urine
- Long term tx reverses growth failure, hepatic issues, and fixes my eyes!
- At risk for learning disabilities
What’s my disorder?

Hereditary fructose intolerance aka Aldolase B intolerance

3. I was doing just fine, minding my own business, until I started munching on these (yummmm!)

- Then I had a seizure and decided I didn’t like them anymore!

2. Labs: prolonged clotting time, low albumin, elevated transaminases and bilirubin

1. Must rid diet of all sucrose, fructose, sorbitol*

- Suspect if urinary-reducing substance during an episode found to be fructose
Oxidative Phosphorylation Diseases and Disorders of Pyruvate Oxidation

Mitochondrial DNA disorders are maternally inherited AR or X-linked!
What’s my disorder?

- I am maternally inherited
- Typical presentation in late childhood-adulthood

- Epilepsy
- Cerebellar ataxia,

- Myoclonic jerks at rest which increase with movement
- And these →

Myoclonic Epilepsy with Ragged Red Fibers (Mitochondrial disorder of oxidation)
What’s my disorder?

- I am AR
- I have:
  - Decreased deep tendon reflexes
  - Impaired cerebellar function
  - Impaired vibratory and proprioception
  - DM
  - Hypertrophic cardiomyopathy
- I account for half of all cases of ataxia*

Friedrich ataxia
Mucopolysaccharidoses

All of them have coarse facies!
And umbilical hernias
Screen with urine glycosaminoglycans
What’s my disorder?

1. My disorder is AR
2. Diagnosed within first 2 years of life
   - I have a big head (>95%) and communicating hydrocephalus, coarsened facial features, midface hypoplasia, and a large tongue
3. Those like me have frequent URIs early on
4. We typically stop growing well after 12 moa and have progressive MR
5. I’m at risk for atlantoaxial subluxation*
6. ↓ alpha-L-iduronidase activity in WBCs
7. Oh, and we have corneal clouding* and deafness
8. Prognosis related to my cardiac involvement*

Type 1 - Hurler
Other mucopolysaccharidoses

- **Sanfillippo-**
  - Inability to catabolize heparin sulfate
  - Diagnosed at age 4-5 yrs,
  - Severe CNS and mild somatic disease, no corneal clouding
  - Phase 1- dev delay with recurrent URIs, diarrhea
  - Phase 2-challenging behavior/aggression*, no concept of danger
  - Phase 3- swallowing dysfunction
  - Death by early 20s

- **Morquio-**
  - Defect of glucose-6-sulfatase: defective degradation of keratan sulfate
  - Short trunk dwarfism, corneal deposits, odontoid dysplasia*
  - Normal intelligence, are not dysmorphic!
What’s my disorder?

4  ➤ My disorder is XLR
    ➤ Only males are affected (rare female with translocation)
    ➤ Dx usually by 2 years of age
    ➤ We have learning difficulties, middle ear disease, hernias, coarse facial appearance, diarrhea, joint stiffness, HSM

3  ➤ A nodular rash around scapulae and extensor surfaces is pathognemonic*

2  ➤ My eyes are normal*

1  ➤ My heart is healthy

Type II- Hunter
Lipid Storage Diseases (Sphingolipididoses)

True lysosomal disease
What’s my disorder?
Gaucher type 1

6 ▶ No CNS involvement, only visceral*

5 ▶ My doctor randomly found splenomegaly* during an exam!
   ▶ I will never have a splenectomy- it would cause increased storage in the lysosomes in my bones (ouch!)

4 ▶ Speaking of bones, I have a lot of “growing” pains*

3 ▶ And I bruise easy (I'm predisposed to thrombocytopenia, ya know)

2 ▶ Xrays demonstrate osteosclerosis and lytic lesions

1 ▶ I have a deficiency of glucocerebrosidase
   ▶ Enzyme replacement therapy helps me!
What’s my disorder?

My disorder is AR

5. My mom says that as a baby, I startled very easily* and I had quick extension of my arms and legs with clonic movements

4. I had axial hypotonia, but extremity hypertonia and hyperreflexia

3. Lots of auditory stimulation will give me a seizure

2. But my belly is fine!

1. Like 90% of those like me, I have fruits in my eyes*?!?
   - I’m 3 now: Unfortunately I’m blind and do not respond to stimuli
   - I have a deficiency of the hexoaminidase A enzyme
What’s my disorder?

My disorder it XLR
  - The only one!*

When I hit puberty, I started having episodic pain in my hands and feet (aka acroparesthesias*)

I have fever and a increased ESR with these crises

Heat exposure sets off my pain crises

I also don’t sweat much*

As I was completing my teen years, I developed angiokeratomatas* (individual, ectatic blood vessels covered with few layers of skin)

If you check my urine, you will find maltese crosses*

My disorder was confirmed by finding low levels of lysosomal galactosidase in my plasma, leukocytes, and cultured skin fibroblasts

I also have orange colored skin lesions

Fabry Disease
What’s my disorder?

1. I have supranuclear vertical gaze palsy* (which is apparently super common!) and ataxia
2. I got sick around 3-5 years of age
3. I freeze when I’m scared, and I fall asleep at a moment’s notice! *

- My disorder is AR
- I don’t really have a lysosomal enzyme disorder, my problem is really due to routing of cholesterol esters within and through the lysosome → I have a lot of extra cholesterol
- Neimann pick disease Type C
Miscellaneous metabolic disorders
What’s my disorder?

1. I have a peroxisomal disorder
2. Onset ranges from birth to 1-2 years
3. It is progressive with a loss of skills

3. I have a pretty classic look: a high forehead, epicanthal folds, broad based nasal bridge, anteverted nares and micrognathia

2. I suffer from abnormal liver function

1. You’ll find calcific stippling of my patella and epiphyses of my long bones

1. My disorder was confirmed by finding abnormalities of VLCFA (peroxisomal enzymes normally oxidize those fatty acids!)

Zellweger
What’s my disorder?

1. There is an impairment in the uptake of copper
   - Low serum copper and ceruloplasmin levels after the 1st week of life, tissue copper level is high

2. My hair and eyebrows sparse with little pigment and easily broken

3. I have SDH and retinal hemorrhages but I haven’t been abused!!!

4. I have progressive neurodegeneration

5. Under the microscope you’ll find “pili torti”

6. Neonatally: premature, temp instability, hypothermia, hypotonia, hypoglycemia,

- X-linked
What’s my disorder?

Smith-Lemli-Opitz

1. Elevated levels of 7-dehydrocholesterol (cholesterol is normal to low)
   - Tx with dietary cholesterol and bile-acid supplements

2. Characteristic features - microcephaly, hypertelorism, broad nasal tip, cleft palate, low set ears, narrow bifrontal diameter, ptosis, anteverted nostrils, micrognathia
   - MR

3. Clinically range from isolated 2/3-toe syndactyly with developmental delay to severely malformed fetuses that die in utero

4. Defect in cholesterol synthesis, AR
   - Cholesterol is important in embryogenesis!
What’s my disorder?

- X-linked disorder of purine metabolism
- Deficiency of HGPRT
- Renal stones and gout due to increased UA production
- Choreiform movements
- Males are normal at birth and by age 2-3 years, self-mutilation (bite lips and fingers)

Lesch-Nyhan Syndrome
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Have a great day!
Noon: Everyone is off... Enjoy!!

No matter how hard you try...

you will never be this happy