Approach to Inborn Errors of Metabolism

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Goals for this lecture:

- Discuss acute/emergency management of IEMs.
- Review broad categories of IEMs.
- Focus on Board favorite zebras.
- Complete the Board prep. Objectives in most recent 2006 edition.
- Integrate the “Laughing your way through Boards” tips.
- Have fun with this usually stressful topic.
What we WON’T DO:

- Memorize metabolic pathways.
- Mention, think of, or utter the enzyme $\alpha$-ketoglutarate dehydrogenase complex.
- Laugh at, throw bagels or coffee at, or otherwise mock Drew.
- Discuss the adverse sequelae of the Eagle’s previous decision to recruit T.O.
IEM Board/Prep Goals:

- Recognize
  - Urea Cycle defects
  - Organic acidemias
  - S+S of CHO disorders
  - S+S of Galactosemia
  - S+S of hyperinsulinism
  - Glycogen Storage Dz
  - Lipoprotein Disorders
  - Gaucher + Lipid Storage Dz
  - S+S of Tay-Sachs
  - S+S of Fatty Acid and Carnitine metabolism

- Inheritance patterns
- Indication for genetics
- Eval of hypoglycemia
- Eval of acidosis
- Vitamin Rx for enzyme disorders
- Treat Hypoglycemia
- Natural Hx of PKU
- Plan/diet for PKU
- Manage Glycogen storage diseases- Type 1
IEM- Index of Suspicion:

- Rapid deterioration in an otherwise well infant.
- Septic appearing infant or abnl sepsis such as E.coli.
- Failure to thrive.
- Regression in milestones.
- Recurrent emesis or feeding difficulty, alterations in respirations, abnl urine/body smell, changing MS/lethargy, jaundice, sz, intractable hiccups.
- Can masquerade like pyloric stenosis.
- Dietary aversion- proteins, carbs.
Basic Principles:

- Although individually rare, altogether they are 1:800-5000 incidence.

- Broadly Defined: An inherent deficiency in a key metabolic pathway resulting in
  - Cellular Intoxication
  - Energy deprivation
  - Mixture of the two
History and Antecedent Events:

- Catabolic state induction (sepsis, fasting, dehydration)
- Protein intake
- Change or addition of PO proteins, carbs, etc... in formula
- **Gotta ask- Consanguinity
- FHx of SIDS
Assessment:

- **Detailed H+P**
  - Describe sz
  - Fevers
  - Milestones
  - FHx
  - Mom’s GsPs
  - NAT questions

- **Dysmorphology does not r/o IEMs**

- **Physical Exam:**
  - Vitals
  - Level of alertness
  - Abnl activity/mvmts
  - CV- perfusion
  - Dysmorphology, hair, smell, eyes-cornea
  - Abdo- HS megaly
  - Neuro- DTRs, tone, etc
  - Skin- bruise, pigment, color
Emergency Management:

- Can be life threatening event requiring rapid assessment and management.

  - ABC’s
    - ABG-acidosis
    - BMP, Ca and LFTs
    - NH4
    - Lactate, Pyruvate
    - CBC, Blood Cx if uncertain
    - Coags- PT/PTT
    - UA-ketones, urine reducing substances, hold for OA/AAs
    - Newborn scam results
    - LP- r/o Meningitis, but send lactate STAT, AAs, hold tubes for future
    - Drug tox screen if indicated.
    - **Hold spun blood or urine sample in fridge for later if possible.
      - **ABG, Lactate are iced STAT samples
      - **NH4 should be free flowing, arterial sample
Emergency Management:

- Correct hypotension.
- NPO, reverse catabolism with D5-D10 1-1.5 x maint.
- Correct hypoglycemia.
- Correct metabolic acidosis.
- Dialysis, lactulose if High/toxic NH4
  - (nl is <35μmol/L)
- Search for and treat precipitants; ie: Infection, dehydration.
- Low threshold for Sepsis w/u + ABx if uncertain.
- Pyridoxine for neonatal sz. if AED no-response
- Ativan, Versed, AEDs for status epilepticus.
Some quick supplements:

- **Carnitine** for elimination of Organic Acid through creation of carnitine esters.
- **Sodium Benzoate, Phenylacetate** for Hyperammononemia elimination.
Stable Patient, Now what?
You could memorize some of these:
The Daunting Differential List:

- **Transient Hyperammonemia of Newborn**
- **Inborn Errors of Metab:**
  - Organic Acidemias
  - Fatty Acid Oxidation def
  - Urea Cycle Defects
  - Amino Acidurias
  - Non-ketotic Hyperglycinemia
- **Molybdenum Cofactor Deficiency**
  - Sulfite Oxidase Deficiency
- **Metal Storage Disorders:**
- **Cholesterol Disorders:**
- **Leukodystrophies, other...**
  - Krabbe disease
- **Mitochondrial Disorders**
- **Glycogen Storage Disorders**
- **Hyperinsulinism**
- **Carbohydrate Disorders**
- **Lysosomal Disorders**
  - Mucopolysaccharidoses (X-linked Hunter’s, Hurler’s)
  - Gaucher disease
  - Tay-Sachs Disease
- **Peroxisomal Disorders**
  - Zellweger’s (Cerebro-Hepato-renal)
  - X-linked Adrenoleukodystrophy
Patient is stabilized. Now what:

- Broad DDx for IEMs scares people.
- You can group into KEY features.
- Can focus on initial labs = Hyperammonia, hypoglycemia, metabolic acidosis.
- Can focus on Prominent neurologic features.
- Can focus on Dysmorphic features.
- If these don’t exactly fit, resort back to categories of IEMs and Neurodegenerative Disorders.
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Transient Hyperammonemia of Newborn:

- Markedly high NH4 in an infant less than 24 HOL, or first 1-2 DOL before protein intake occurs.
- Often in context of large, premature infant with symptomatic pulmonary disease.
- Very sick infant.
- Unknown precipitant, unknown etiology (possible slow delayed urea cycle initiation), with potential for severe sequelae (20-30% death, 30-40% abnl devo) if not treated.
- Does not recur after being treated.
Organic Acidemias:

- *Acidotic* with high Gap
- *Urine Ketones* high
- *High to nl* Ammonia
- Often present first 2-7 days of life after dietary protein introduced.
- Drunk appearance in infant.
- *May have low WBC and Plts.*
- Check serum AAs/OAs, Urine AAs/OAs, CSF OAs/AAs.
Organic Acidemias cont:

- **Multiple Carboxylase Deficiency**

  or

- **Defect in Biotin Utilization**

  - Biotin is vital cofactor in many pathways, defect results in:
  - Severe deterioration, dermatitis, alopecia, immune deficiency- candidal skin infections.
  - High NH4, acidemic, ketotic like the others.
  - Dx by enzyme assay.
  - Rx with Biotin 10mg/kg/d PO

**Rocky will get this if he consumes too much Avidin, aka, raw eggs.**
Amino Acidurias:

- **Maple Syrup Urine Disease**
  - Sweet smell of body fluid esp Urine.
  - Classically develops in 1\textsuperscript{st} week of Life.
  - Poor feeding, emesis, lethargy and coma.
  - Periods of Hypertonicity.
  - Secondary Hypoglycemia.
  - Possible Metabolic Acidosis, hyperammonemia
  - **Obtain serum/urine AAs/OAs**
  - Treatment requires rapid removal of Branched chain AAs, often through dialysis.
Amino Acidurias:

- Fresh Urine **Uric acid** and **Sulfite Dipstick** if neurologic abnormalities are present, low uric acid is suggestive for **molybdenum cofactor deficiency and Sulfite Oxidase Deficiency**.
- Don’t forget **PKU**. Basic on newborn scrn, but only does good if results followed up.
For the Boards:

- **Sweaty feet smell**
  - Isovaleric Acidemia, think *ISOTONER* shoes smell

- What defect may present with Pulmonary Embolus?

- **Homocystinuria** - and thereafter may ask which supplement to initiate?

- **Pyridoxine** - due to residual enzyme activity.

- Other names to know:
  - Methylmalonic Acidemia - Rx with large dose *vitamin B12*
  - Propionic Acidemia - RX with *Biotin*. 
Urea Cycle Defects:

- All but one of the disorders is autosomal recessive.
- Symptom free period and then emesis → lethargy → COMA
- Key features:
  - High Ammonia, low BUN
  - Possible Lactic acidosis
  - *Absence of ketonuria*
  - NI to mild low Glucose
- **Treat high ammonia, infuse glucose, send plasma AAs/OAs, urine orotic acid, and plasma citrulline.**
- Infusion of 6ml/kg 10% Arginine HCl over 90 min may help.
- Milder forms may show episodic emesis, confusion, ataxia, and combativeness after high protein meals.
For the Boards:

- Most common Urea cycle defect and also only X-linked:
  - Ornithine Transcarbamylase Deficiency
Fatty Acid Oxidation Defects:

- **Autosomal recessive inheritance**
- Examples are MCAD, LCAD, VLCAD
- Defect in acyl-CoA Dehydrogenase, a mitochondrial duty, and important in fasting state.
- KEY features:
  - Acute attack of life-threatening coma with Hypoglycemia
  - Absence of urine ketones, and reducing substances, nl serum AAs.
  - +/- mild acidosis, or hyperammonemina, elevated LFTs, abnl coags. +/-Hepatomegaly-/+ 
  - Dx with serum Acylcarnitine Profile or fibroblast enzyme assay
For the Boards:

- Fetal Defect in LCHAD may result in Prenatal course complicated by:
  - Maternal HELLP syndrome
Non-ketotic Hyperglycinemia:

- Unique entity in that Glucose, NH4, pH are all normal.
- 4 types with varying ages of onset, however, classic form is Neonatal with onset in 1st week of life.
- Will present just like the other devastating IEMs. Lethargy, emesis, hypotonia, seizures, etc...
- Uncontrolled hiccups.
- Dx with no urine ketones, and Elevated Glycine.
- No effective Rx. Will require diet restriction.
- Long term is a devastating disease.
Carbohydrate related Disorders:
Galactosemia:

- First 1-2 wks of Life: Presents with hypoglycemia, jaundice, emesis.
- Secondary to intolerance of Galactose. Will be in baby’s first meals of breast milk or lactose containing formulas.
- Also index of suspicion for GramNeg or E.coli sepsis.
- Dx assisted by Non-glucose reducing substances in urine.
- Confirmation by Galactose-1-PO uridyl transferase activity in RBCs.
- Adverse sequelae include Cataracts, MR, persistent liver disease.
For the Boards:

- Which is worse?
  - Essential Fructosuria
  - Inherited Fructose Intolerance

- **Inherited Fructose Intolerance**
  - Occurs after ingestion of Fructose (sucrose= glucose + fructose)
  - Severe and life threatening intoxication of $\text{F}_\text{1-PO}_4$.
  - Presents with emesis, seizures and profound illness after ingestion of fructose.
  - May also present similar to Galactosemia.
  - Life long avoidance of fructose.
Glycogen Storage Disorders:

- **Type 1= Von Gierke’s:**
  - Shortly after birth: Severe lifethreatening Hypoglycemia
  - Lactic acidosis –due to isolated glycolysis of G6Po
  - Hyper-uricemia, hyper lipidemia
  - Increased association with epistaxis
  - *Hepatomegaly
  - **Adverse response to Glucagon with worsening Lactic acidosis

- Management requires IV glucose, and then as outpt, close NG corn-starch or glucose solution administration to achieve close to nl glucose homeostasis.

- Frequent snacks and meals. Continuous nighttime glucose infusions up to the age of 2.
Glycogen Storage Disorders:

- **Type 2 - Pompe’s disease:**
  - Normal Glucose
  - Do to an accumulation of glycogen in lysosomes.
  - **Ancient city of Pompeii was destroyed by Mt. Vesuvius- 79 AD**
  - Manifested by massive Cardiomegaly, Hepatomegaly, Macroglossia.
  - Fatal If results in CHF.
  - Limited therapies in Neonatal Variant.
    - Attempts at enzyme replacement ongoing.
Mitochondrial Disorders:

- Emerging spectrum of diseases with lifetime variation of presentation.
- Infantile/Neonatal: may present with encephalopathic picture, regressed milestones, cerebral cortical atrophy.
- Generally lab findings of:
  - Lactic Acidosis
  - NL to low serum pyruvate, in comparison to Lactate
  - NL organic acids.
  - *** Important to check CSF values of the above ***
Leigh’s Disease

- AKA- Subacute necrosing encephalopathy
- Due to defects in the mitochondrial electron transport chain.
- May have devastating presentation with significant developmental regression.
- Unfavorable natural history.
- May respond to host of supplements.
- **Other Mitochondrial disorders for completion sake**
  - MELAS, MERRF, Leber’s HON
Leukodystrophies:

- **Krabbe disease:**
  - **Type 1-** "Infantile" = irritability, hypertonia, hyperesthesia, and psychomotor arrest, followed by rapid deterioration, optic atrophy, and early death
  - **Type 2-** Late infantile
  - **Type 3-** Juvenile
  - **Type 4-** Adult

- A demyelination disorder due to CNS accumulation of galactosylceramide.

- Diagnosis: supported by cortical atrophy on CT/MRI, **High CSF protein** and definite evidence of deficient **GALC assay** in WBCs or skin fibroblasts.
Lysosomal Disorders
Focus on key differences:

- **Gaucher Disease:**
  - Infantile vs chronic juvenile
  - Organomegaly
  - Bone pain
  - Easy bruising
  - **low Plts, osteosclerosis, and lytic bone lesions**
  - MNEUNOMIC = “Clumsy Gaucho cowboy”

- **Tay-Sachs Disease:**
  - Progressive neurologic degeneration in first YOL and death by age 4-5 yo
  - AR inheritance with classic Jewish Ashkenazi relationship.
  - Increased startle reflex
  - Cherry red macula
  - Macrocephaly
Peroxisomal Disorders

- **Zellweger Syndrome**
- aka: Cerebro-hepato-renal syndrome
- Typical and easily recognized dysmorphic facies.
- Progressive degeneration of Brain/Liver/Kidney, with death ~6 mo after onset.
- When screening for PDs, obtain serum Very Long Chain Fatty Acids - VLCFAs
Further Evaluation in IEMs:

- **Head CT, MRI, Ophtho, Audio, EKG, EEG**
- Genetics consultation.
- Peds Neuro consultation.
Random Questions for the Boards:

- Amino Acids responsible for MSUD?
  - Valine, Leucine, Isoleucine

- Name 1 of the 3 classic Metal Storage disorders?
  - Menke’s Kinky Hair Syndrome (X-link recessive)
  - Wilson’s Disease
  - Neonatal Hemachromatosis

- Lysosomal storage disease associated with Adrenal Gland calcifications?
  - Wolman Disease
    - Fatty acid deposits, nl lipid panel
    - **Mneumo** = Wool Man Disease → white wool deposits.
Recognize that Smell:

- **Musty or Mousy:**
  - PKU
  - Boiled Cabbage
  - Tyrosinemia or hypermethioninemia
- **Maple Syrup**
  - maple syrup urine disease
- **Sweaty feet:**
  - isovaleric acidemia or glutaric acidemia type II
- **Cat urine**
  - multiple carboxylase deficiencies (Biotin deficiency)
Follow up Questions?

- Name some classic Mucopolysaccharidosis?
  - Hunter’s (X-linked, no corneal clouding)
  - Hurler’s (presence of Corneal clouding)
  - Morquio Syndrome (nl IQ, short, cloudy cornea) *tattoo on FI

- How are mucopolysaccharidoses Diagnosed?
  - Urine MPSs, definite with Skin Fibroblast Bx

- How to treat **Neonatal Hyperinsulinism**?
  - **Diazoxide** - inhibits pancreatic B-cell insulin secretion.
  - Child Dx with PKU, now diet restricted, but with progressive neuro deterioration. What else might be deficient?
  - **Tetrahydrobiopterin (BH4)**
Finally and to wet your appetite for Sat:

- Name this syndrome and the associated metabolic defect.
- **Smith-Lemli-Opitz Syndrome:** due to defect in **cholesterol synthesis**.

![Image A](image1.png)

![Image B](image2.png)
For Reference:

- AAP Guidelines to IEMs. DOI: 10.1542/peds.102.6.e69 *Pediatrics*
  1998;102;69- Barbara K. Burton
Quick Algorithms:

METABOLIC ACIDOSIS WITH INCREASED ANION GAP

- Normal lactate
  - Abnormal organic acids
    - ORGANIC ACIDEMIA
      - Dicarboxylic aciduria
        - FATTY ACID OXIDATION DEFECTS
          - GSD TYPE I, FRUCTOSE 1,6-DP DEFICIENCY; PEP CARBOXYKNASE DEFICIENCY

- Elevated lactate
  - Normal organic acids
    - Elevated pyruvate: normal L-P ratio
      - Hypoglycemia
    - No hypoglycemia
      - RESPIRATORY CHAIN DEFECTS; PYRUVATE CARBOXYLASE DEFICIENCY

NEONATAL HYPERAMMONEMIA

- Symptoms in first 24 h of life
  - Premature
    - THAN
      - INBORN ERRORS OF METABOLISM (i.e. organic acidemia or PC deficiency)
  - Full-term
    - Acidois

- Symptoms after 24 h of age
  - No acidosis
    - UREA CYCLE DEFECTS
      - PLASMA AMINO ACIDS
        - Absent citrulline
          - Urine orotic acid
            - Argininosuccinic aciduria
        - Citrulline moderately elevated; ASA present
          - Citrulline markedly elevated, no ASA
            - Citrullinemia
  - ORGANIC ACIDEMIAS
    - CPS deficiency
    - OTC deficiency