Metabolic Emergencies and the Pediatrician

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INHERITED METABOLIC DISORDERS—HOW THEY MAY PRESENT ACUTELY

- Malformations
- Lethargy/Coma
- Seizures
- Sepsis-like (Hypoperfusion, shock, acidosis)
METABOLIC DISORDERS—LAB ABNORMALITIES (simple tests)

• Hypoglycemia
• Acidosis
• Hyperammonemia
• Adrenal Insufficiency
• Hypocalcemia

MALFORMATIONS THAT MAY HERALD A METABOLIC EMERGENCY

• Ambiguous genitalia
• Congenital heart defects, esp cono-truncal defects
• Macrocephaly
• Characteristic facies
A few items relating to history

- Most of these conditions are autosomal recessive—family history is usually negative except for siblings.
- The major X-linked disorder that can present as an emergency is OTC (ornithine transcarbamoylase) deficiency, a urea cycle (hyperammonemia) disorder.
- Many of the disorders covered in this talk can be detected by newborn screening. NEVERTHELESS, even if NBS is normal, do the workup as if NBS hadn’t been done.

Ambiguous Genitalia

- Chromosomes aren’t gender, which isn’t the same as appearance, sex of rearing, or sexual identity/orientation.
- Ambiguity—virilized female, or incompletely virilized male?
- Most important question: Are testes present?
What to think of next?

• Primary malformation OR
• CONGENITAL ADRENAL HYPERPLASIA?
  – Common form—excess androgen = virilizing
  – Genetic females will be more obvious than genetic males
  – BOTH are vulnerable to adrenal (Addisonian) crisis—shock, sepsis, hyponatremia, hypoglycemia

CAH--2

• Less common forms—
  – Androgen insufficiency
  – hypertensive
HYPOGLYEMIA

• Appearance, age, timing, ketosis, acidosis, febrile illness are all clues to likely etiology

HYPOGLYCEMIA—APPEARANCE

• Prenatal overgrowth—symmetrical
• History of maternal hyperglycemia
• = IDM.
• Malformations—increased risk of all, including CHD, cleft lip +/- cleft palate, NTDs.
• PLUS specific malformations—proximal femoral hypoplasia/unusual facies syndrome, VATER/VACTERL;
• Hypoglycemia is rapid—hyperinsulinism despite falling blood glucose.
Hypoglycemia

• “Nesidioblastosis”—hyperinsulinism not due to IDM, BWS, etc.
• Diagnosis may be difficult
• Insulin/glucose (IU/ml / mg/dL) > 0.25 WHEN GLUCOSE IS IN NORMAL RANGE—DOES NOT APPLY WITH HYPOGLYCEMIA.

HYPOGLYCEMIA--APPEARANCE

• Intrauterine overgrowth, asymmetry, macroglossia, omphalocele, visceromegaly, etc. =
• Beckwith-Wiedemann syndrome.

• Hypoglycemia due to pancreatic overgrowth;
• Etiology—chr 11 abnormality in imprinted region.
HYPOGLYCEMIA

• Problems with glycogenolysis
• Problems with gluconeogenesis
• Problems with both

• Ketosis?
  – Infants—mainly beta-hydroxybutyrate = dipstick will be NEGATIVE; POSITIVE is unusual—think of IEMs
  – Older—Acetoacetate to be expected—NEGATIVE points to problems with lipolysis

KETOSIS—2

• With hypoglycemia, expect LARGE ketones. Hypoketosis is a huge clue to lipolysis defect
HYPOGLYCEMIA—LAB TESTS

- Blood glucose and ketones, Chem C/S;
- Plasma carnitine and acylcarnitine profile (explain)
- Insulin and c-peptide
- Plasma amino acids, urine organic acids
- Hormones—thyroid, hGH, cortisol, ACTH
- Didja tube (plasma)
- Others?

TIMING OF GLUCOSE SOURCES

- For 2 hours after feeding—glucose in meal
- Next several hours—glycogenolysis
- Gluconeogenesis after that.
ACIDOSIS

- Physical findings
- Tachypnea, hyperpnea
- May be accompanied by ketosis
- ONLY FOUR ACIDS ARE THE PRIMARY ACIDS INVOLVED IN ACIDOSIS, SO ALL BUT ONE ARE HIGHLY NON-SPECIFIC.

THE FOUR ACIDS OF METABOLIC ACIDOSIS

- The ketone bodies—beta-hydroxybutyrate (2-oxobutyrate), and acetoacetate
- Lactate
- And the acid that points to a specific diagnosis—METHYLMALONIC.
- (There are other acids which accumulate in renal failure, and there are toxins that lead to acidosis (methanol, for example), but they are for another time.)
HYPERAMMONEMIA

• Tachypnea → respiratory alkalosis.
  – (unlike hypoxia, metabolic acidosis, etc. where we don’t see pH > 7.45!)
• Lethargy and hypotonia, but hyperreflexia
• Coma, apnea, seizures
• Cerebral edema
• CSF hyperammonemia may be worse than what is measured in the periphery

HYPERAMMONEMIA 2

• Pure hyperammonemia = UREA CYCLE DISORDERS
• With keto/lactic acidosis = ORGANIC ACIDURIAS, FATTY ACID OXIDATION DISORDERS (INCLUDING MITOCHONDRIAL DYSFUNCTION)
• With major liver dysfunction—probable generalized hepatic problem—-hepatitis.
SEIZURES

• Hyperexcitable state—may be accompanied by altered consciousness, coma
• Generalized vs localized
• Substrate insufficiency—glucose, creatine, energy
• Toxin—ammonia, GLYCINE, leucine (MSUD), etc.

COMA

• Generalized. Brainstem (central arousal mechanisms) OR bilateral cortical injury/dysfunction.
• Same as for seizures—lack of substrate, presence of toxin.
• NEUROTRANSMITTER DEFECT, ESP WITH MOVEMENT DISORDER. FOLATE, BIOPTERIN, ETC. DEFICIENCY
Some examples--1

• 16-month-old girl, previous healthy.
• Otitis media yesterday, T 104 (40 C)
• No breakfast, grumpy→ lethargy
• Comes to ER
  – RR 50, deep. R OM, general exam otherwise unremarkable.
  – pH 7.25, lactate 2.0 mg/dL, ammonia 250 mM, glucose 30 mg/dL, urine small ketones.

Examples--2

• 5 day old boy
• Unremarkable pregnancy
• D/C day 2, seemed OK, but never seemed quite awake. Feeding +/- OK, acc to nurses
• PE—hypotonic, barely arousable, doesn’t open eyes, poor nippling from bottle.
• Afebrile, RR 50 (quiet), ABG normal, ammonia 35, glucose 85, anion gap normal, neg urine ketones.
Example 4

• 7 day old girl. OK at birth. Home with mother on day 2. Fed well till yesterday. Now lethargic, shocky. No cataracts
• Lethargic, jaundiced, liver firm, 7 cm below RCM;
• Bicarb 12, low BP, WBC increased (neutrophils and bands), bili—total 20, direct 10, ind 10.
• Urine—trace glucose, 4+ reducing substances
• Blood culture *E. coli*. Also CSF.

Example 5

• Term female infant
• Lethargy on day 8.
• Tachypnea
• Liver 6 cm below RCM
• Na 140, K 4.5, HCO3 12, Cl 108, Glu 55
• Urine 4+ ketones
• Lactate 5.0, ammonia 200
Example 5 part 2

• Anything else you might note without a lab?
  • [Fontanelle, retina, reflexes, odor]
• AAs
• OAs

CURRENT ARKANSAS NEWBORN SCREENING

• NOT Metabolic:
  – Cystic fibrosis (Trypsinogen/DNA)
  – Hemoglobinopathies
  – Congenital hearing loss
  – Hypothyroidism (sort of)
• And Coming –
  – Cyanotic heart disease
  – Severe combined immune deficiency (SCID)
CURRENT ARKANSAS NEWBORN SCREENING--2

• “METABOLIC”
  – Congenital adrenal hyperplasia (17-OH progesterone–)
  – Galactosemia (GALT/UDPGT enzyme activity)
  – Biotinidase
  – Amino acids by tandem mass spectrometry
  – Acylcarnitines

TANDEM MASS SPECTROMETRY FOR NBS

• Amino Acids—not all—
  – Phenylalanine (PKU +)
  – Tyrosine (Tyrosinemia)
  – Leucine/Isoleucine (Maple Syrup Urine Dis)
  – Methionine (Homocystinuria +)

• Acylcarnitines
  – Products of Fatty Acid Oxidation and
  – Organic Acidurias (later steps of AA metabolism)
GOTCHAS

• A normal newborn screen, like any other test, isn’t 100% = SEND WHATEVER TESTS ARE INDICATED BASED ON PATIENT.
• Fenugreek produces sotolone, the odorific substance of maple syrup and MSUD—so odor + normal baby + normal NBS is probably NOT MSUD. Always check if worried. Ear wax traps sotolone—sniff!!

PEARLS--1

• The anion gap is VERY useful
  \[ \text{Na} - (\text{Cl} + \text{HCO}_3) = \text{AG} \ (\text{nl} < 12-15) \]
  – pH less so, as patients can hyperventilate to normalize it.
• Ketones (pos dipstick) are surprising in young infant; lack of ketones are surprising in anyone older with hypoglycemia.
PEARLS--2

- Lethargy, Hypotonia + HYPERREFLEXIA—Think of ammonia, glycine
- Lethargy + ALKALOSIS → Hyperammonemia
- Lethargy + ALL ROUTINE LABS NORMAL → Glycine encephalopathy

PEARLS--3

- Maternal history of fatty liver (HELPP, etc.) CAN indicate baby affected with LCHAD deficiency
- Some disorders of long-chain fats become LESS prominent on follow-up testing—CALL IF THERE ARE CONCERNS
- Very-long-chain Acyl-CoA dehydrogenase == enzyme of fatty acid oxidation (Mito); Very Long Chain fatty acids—peroxisomal disorders
PEARLS--4

• Acute encephalitis vs. diffuse tumor—THINK OF X-LINKED ADRENO-LEUKODYSTROPHY (Lorenzo’s Oil disease)--This disorder is X-linked; other forms are adrenomyeloneuropathy; and in females there may be no sx, various (milder) sx of cord or long tracts,