Hypoglycemia: Pediatric Board Review

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Definition

- Hypoglycemia is defined as serum glucose less than 50 mg/dL in older children and neonates
  - Some define it as less than 60 mg/dL
  - Goal is to protect the brain!!
Susceptibility

- Neonates & children have limited glucose homeostasis in comparison to adults
  - Smaller stores of liver glycogen & muscle
  - Large demands of glucose consumption related to larger brain-to-body-mass ratio
    - Glucose production & utilization = 5-7mg/kg/min in infants and children vs. 1-2mg/kg/min in adults
Fasting Adaptation

- Hypoglycemia is a failure of fasting adaptation
- Adaptation in children is the same as adults
  - Faster and More limited
    - A 10 kg infant has 60% of the caloric needs of an adult but only 15% of the fuel stores
    - After a 6 hr Fast: normal neonates have 10% chance of BG < 30 & 30% chance of BG <50
Timing

- Hypoglycemia most commonly seen in pediatrics in the **fasting state**
  - **Fed state** = exogenous glucose used by & stored in tissues; insulin ↑ & glucagon ↓
  - **Fasting state** = glycogenolysis then gluconeogenesis and fatty acid oxidation
Normal Carbohydrate Metabolism

- Insulin suppresses gluconeogenesis, glycogenolysis, lipolysis
  - responsible for storage of glucose by production of glycogen, AA into protein, & lipids into TG
  - Suppresses ketone bodies
- During fasting times, insulin secretion should be SUPPRESSED
Counter-regulatory Hormones

- GH
  - Transient effect of decreasing BG but then insulin suppression
- Cortisol
  - Insulin suppression
- Glucagon
  - Stimulates glycogenolysis & gluconeogenesis
- Epinephrine
  - Stimulates glycogenolysis & gluconeogenesis
Defenses against Hypoglycemia in the Fasting State

1. **Glycogenolysis** – triggered by drop in insulin, increase in glucagon, epi
   - Infants: 4 hours
   - Older child: 8 hours

2. **Gluconeogenesis** – accel by Cortisol
   - Major precursor is alanine – muscle breakdown

3. **Fatty acid oxidation** – triggered by all counter-reg hormones
   - Ketones used by brain and muscle – decreases use of sugar by these organs, sparing for others and preventing muscle breakdown
   - In infants, appears within 12-18 hours, in older kids, 18-24 hours
   - Urea also produced
Glycogenolysis

Muscle breakdown

Gluconeogenesis

Lipolysis
Early Hypoglycemia

- Hyperinsulinism – NO KETONES
  - Congenital (nesidioblastosis)
    - 60% present in the 1st week of life
    - Defects in β cell regulation of insulin secretion
  - Factitious
  - Insulinoma- VERY rare in infants, more common in later childhood but still MUCH less common than in adults; MEN-1(3 P’s)

- In a neonate, think of IDM, stress, premature, SGA, Beckwith-Weidemann
IDM

- Macrosomia
- IUGR if very severe – due to maternal renovascular disease
- RDS, TTN
- Hypocalcemia (due to hypomagnesemia causing impaired PTH release)
- Polycythemia – chronic fetal hypoxia, can lead to hyperbilirubinemia
- Cardiac - VSD, TGA, cardiomyopathy
- **Skeletal – Caudal Dysplasia, regression**
- Neural – neural tube defects, spinal bifida, anencephaly
Beckwith-Weidemann Syndrome

- microduplication mutations in the 11p15.5 region
- maternal copy of BW gene is silenced during gametogenesis & only the paternal copy expressed
- offspring with BWS have mutation passed from their father
- offspring who inherit BW gene mutation from their mother are asymptomatic carriers
  - can pass the mutation to their offspring
Beckwith-Weidemann Syndrome

- Macroglossia
- Gigantism-large length & wt
- Omphalocele
- Hemihypertrophy
- Hepatomegaly
- Cardiomegaly
- Ear creases

- Pancreatic cell hyperplasia = life-threatening hypoglycemia
- Wilms tumors
- Hepatoblastoma
- Adrenal Carcinoma
- Gonadoblastoma
Early Hypoglycemia

- Glycogen Storage Disease type 1 – Von Gierke’s
  - Defect in glucose 6 phosphatase
  - Terminal step of both hepatic gluconeogenesis and glycogenolysis, so no chance for defense against hypoglycemia
  - Massive hepatomegaly
  - Lactic acidosis – tachypnea
  - Hyperuricemia
  - Treatment: frequent snacks, meals, corn starch
Early Hypoglycemia

Glycogen Storage Disease 3

- Debrancher enzyme
- Hypoglycemia less severe as they retain gluconeogenesis
- Usually present in later infancy, childhood
- Will make ketones used by brain
- Hepatomegaly, FTT
- No lactic acidosis
GSD II

- Pompe Disease
- Lysosomal breakdown of glycogen
- Hypoglycemia and acidosis NOT a part of it
- The build-up of glycogen causes progressive muscle weakness throughout the body and affects heart, skeletal muscles, liver, CNS
- Story is usually a < 1 month old who is floppy, FTT, has a big liver and macroglossia
- Have cardiomegaly, “hard muscles”
Galactosemia

- Defect in galactose 1-P uridyl transferase
- Galactose builds up = toxic
- Exposure to galactose results in acute deterioration (after 1st few days of life) – postprandial hypoglycemia
- Liver dysfunction
- Coagulopathy
- Poor feeding
- Neutropenia
- Hyperbili
- Reducing substances
- Cataracts – reversible with diet change
- E coli sepsis
- Tx: avoid galactose (soy)
Disorders of Gluconeogenesis

- Fructose 1,6 diphosphatase deficiency
- Hypoglycemia does not develop until fasted beyond glycogen stores (presents later than GSD type I)
- Lactic, keto-acidosis
- Hepatomegaly = lipid storage
- Hyperuricemia
- Tx: avoid fasting
Fructose Intolerance

- Defect in Fructose 1 phosphate aldolase
- In the absence of fructose ingestion, pts are normal
- After juice/fruit introduced, have episodes of hypoglycemia, vomiting, abdominal pain after feeds
- Often avoiding juice/fruit is self-learned
Later hypoglycemia

- Disorders of Fatty Acid Metabolism
  - Fatty acid or Carnitine transport of the plasma membrane or mitochondria
  - B-oxidation defects
  - Electron transport defects
  - Defects in ketone body synthesis and utilization
  - Become clinically apparent only after prolonged periods of fasting
  - LOW KETONES
  - HIGH FREE FATTY ACIDS
  - Alteration to acyl carnitine profile
  - MCAD most classic example
Later hypoglycemia

† Ketotic hypoglycemia
  † Disorders of substrate – alanine for gluconeogenesis
    † 18 mo-5 years, and remits by 8-9 years
    † Morning hypoglycemia with ketosis/ketonuria after overnight long fast in thin (low muscle mass) child

† Other disorders of gluconeogenesis
  † Alcohol intoxication:
    † liver metabolizes alcohol as a preferred fuel
    † generates reducing equivalents during oxidation & alters NADH/NAD ratio necessary for gluconeogenesis

† Salicylate intoxication:
  † augments insulin secretion & interferes with gluconeogenesis
Hormonal deficiencies – cortisol, GH

- Contribute to body’s response to hypoglycemia, so leads to disordered response
- Variable ketosis
- Look for other signs of hypopituitarism: central incisor, microphallus
- Adrenal Insufficiency
Critical sample

- BG <50 in late infancy, older child
  - Serum BG
  - Insulin
  - Cortisol
  - Growth hormone
  - Urine/serum ketones
  - Lactate, pyruvate
  - Free fatty acids
  - Ammonia
  - Acyl carnitine profile
  - Serum AA, Urine OA
Hypoglycemia

Acidosis

- Lactic Acidosis
  - GSD 1
  - Disorders of Gluconeogenesis

- Ketoacidosis
  - Ketotic hypoglycemia
  - GSD 3, 6, 9, 10
  - GH deficiency
  - Cortisol deficiency

No Acidosis

- Low Ketones High FFA
  - FAO

- Low Ketones Low FFA
  - Hyperinsulinism
You are asked to see a term infant in the newborn nursery at 8 hours of age and consider her transfer to the neonatal intensive care unit. The problems and findings reported to you include: poor feeding, emesis, temperature instability (core temperature of 96°F [35.5°C]), hypoglycemia (whole blood glucose concentration of 25 mg/dL [1.4 mmol/L]), and polycythemia (hematocrit of 70% [0.70]).

Of the following, the physical finding that is MOST likely to accompany these problems is
A. a tuft of hair over the sacral region
B. birthweight of 1,800 g
C. café au lait macule on the left leg
D. iris coloboma of the right eye
E. isolated cleft of the hard palate
A. a tuft of hair over the sacral region – possible neural tube defect
B. birthweight of 1,800 g – SGA, Stress, IDM (can be LGA or SGA), sepsis
C. café au lait macule on the left leg – McCune Albright, NF
D. iris coloboma of the right eye - CHARGE
E. isolated cleft of the hard palate
A newborn female has an open neural tube defect, low-set ears, ventricular septal defect, and rib and vertebral column malformations.

Of the following, the MOST likely maternal condition that was present during this pregnancy is
A. Alcoholism
B. diabetes mellitus
C. Hypothyroidism
D. iodine deficiency
E. syphilis
A. Alcoholism – FAS, flat filtrum, thin upper lip, small 5th fingernail, midface hypoplasia, short palpebral fissures
B. **diabetes mellitus**
C. Hypothyroidism – umbilical hernia, jaundice, constipation, hypotonia, hoarse cry, enlarged anterior fontanelle, thickened eyelid, hypertelorism, thickened protruding tongue
D. iodine deficiency – same as hypothyroidism
E. Syphilis – poor feeding, “snuffles”, mucocutaneous lesions, hepatomegaly
Congenital Hypothyroidism

- Constipation
- Hypotonia
- Hoarse Cry
- Enlarged anterior fontanelle
- Thickened eyelid, hypertelorism
- Thickened protruding tongue
- Umbilical hernia
- Cold skin
IDM

- LGA
- Low tone
- Polycythemic
- Cardiac (VSD)
- Neural (Spina bifida)
- Ortho (caudal regression)
A 4-month-old child is admitted to the hospital for evaluation of failure to thrive and generalized seizures. On physical examination, the child appears wasted and has a protuberant abdomen and marked hepatomegaly. Laboratory evaluation reveals fasting hypoglycemia, lactic acidosis, hyperuricemia, and hyperlipidemia. The boy's parents are first cousins.

Of the following, the BEST long-term management of this disorder is
A. oral dietary supplementation with long-chain fatty acids
B. oral dietary supplementation with protein
C. regular intravenous administration of 10% dextrose in water
D. regular intravenous administration of glucagon
E. regular oral administration of cornstarch
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