Hypoglycemia

Introduction

Clamping of the cord leads to a surge in glucagon in neonates, however, blood glucose continues to decrease within the first 2 hrs of life and stabilizes/increases by 4-6 hours of life due to mobilization of hepatic glycogen stores. During the first 8-10 years of life, the rate of glucose utilization (and production increases), followed by a plateau for the next 5-7 years. Thus, unlike adults, children are unable to maintain a normal plasma glucose concentration even after a short fast of 24-36 hours.

Definition of hypoglycemia

<40 mg/dL, regardless of age. This definition is controversial, however, glucose levels below 40 mg/dL produces hunger and excessive catecholamine response.

Symptoms

- Gen: Irritability, anxiety, hunger, fatigue,
- Neuro: HA, blurred vision, tremors, weakness, confusion, ataxia, stupor, seizures, coma
- GI: abdominal pain,
- Heme/CV: pallor, cyanosis, diaphoresis, tachycardia,
- Resp: tachypnea, lethargy, apnea
- Most symptoms can be explained through stimulation of sympathetic responses. Recurrent severe hypoglycemic episodes can lead to brain damage and intellectual impairment.

Important Aspects of History

- Age
- Dietary Intake: what types of food (carbohydrates, protein, etc), how soon after eating did hypoglycemia develop, amount of food intake
- Child’s PMHx
- Family History: sudden infant deaths, similar problems in family

Evaluation of Suspected Hypoglycemia

(note: if possible, collect these samples before treatment to offer chances of earlier diagnosis)

- Venous sample for glucose, BMP (electrolytes, BUN, Cr), LFTs, lactate, insulin level, C-peptide, growth hormone, and cortisol levels.
- Blood samples for substrates: FFAs, Beta-hydroxybutarate, total and free carnitine, acylcarnitines
- Immediately begin efforts to collect urine (bagged specimen) and send for urinalysis and urine organic acid analysis.
- Check urine for ketones and glucose.

Differential for Hypoglycemia

A good starting point for evaluating hypoglycemia is to divide patients into ketotic or non-ketotic. Normal physiologic response to decreased glucose production is increased mitochondrial fatty acid beta-oxidation and the production of ketones. Ketones provide an indirect indication of whether hypoglycemia is the result of inadequate production or of over-utilization of glucose (insulin-induced over-utilization, associated with low urine or plasma ketones). The history of the relationship of the hypoglycemia to feeding is often helpful. Hypoketotic hypoglycemia developing within several minutes of feeding is typical of hyperinsulinism. Patients with defects in glycogen breakdown, gluconeogenesis, or fatty acid oxidation tend to tolerate short-term fasting much better.
Hypoglycemia can be caused by many primary metabolic defects:

1. Idiopathic (Most common)
   a. Idiopathic Ketotic Hypoglycemia

2. Inadequate Intake

3. Hyperinsulinemia
   a. Congenital Hyperinsulinemia
   b. Beckwith-Wiedemann Syndrome
   c. Transient Hyperinsulinism
   d. Relative Hyperinsulinism in Treatment of DM
   e. Gastric Dumping Syndrome
   f. Islet Cell Adenomas

4. Endocrine Deficiencies
   a. Adrenal Insufficiency
   b. Growth Hormone Insufficiency
   c. Hypothyroidism

5. Glycogenolysis Defects

6. Organic Acidemias

7. Glycogen Storage Defect
   a. Type I
   b. Type III
   c. Type IV

8. Gluconeogenesis Defects
   a. Fructose 1,6-diphosphatase deficiency
   b. Fructose Intolerance
   c. Galactosemia

9. Fatty Acid Metabolism Defects

**IDIOPATHIC KETOTIC HYPOGLYCEMIA**

Most common form of childhood hypoglycemia

**Typical scenario:** Between 19 months and 5 years of age, remits before 8 to 9 years. Hypoglycemia usually in association with intercurrent infections or at times of fasting for 12 hours or more. Children may vomit.

**Causes/Pathophysiology:** Currently idiopathic. The mechanism of hypoglycemia may be that patients do not have appropriate increases in gluconeogenesis in response to low glucose

**Treatment:** Frequent feeding (four to five meals a day) of a high protein, high carbohydrate diet. Parents can be instructed to test children for ketones with urine dip stick.

**Review:** (Huidekoper et al., 2007).

**HYPERINSULINEMIAS (NON-KETOTIC)**

Inappropriate overproduction of insulin. Seen in both infancy and childhood. In the first year of life, can lead to brain damage and intellectual impairment if not diagnosed and treated swiftly.

1. Congenital hyperinsulinemias

**Typical scenario:** Presentation early in life. Labs show elevated insulin with low ketones in blood and urine. Associated with elevated ammonia in hyperammonemia-hyperinsulinism.

**Causes/Pathophysiology:** Defect of pancreatic beta cell KATP channel (ABCC8, KCNJ11), glucokinase, short chain acyl-CoA dehydrogenase; glutamate dehydrogenase mutations are responsible for hyperammonemia-hyperinsulinism (brief summary: Hussain et al., 2007, Glaser, 2010).

**Treatment:** Glucose IV. Diet. Medical management to increase glucose such as diazoxide, glucagon, cortisol, somatostatin, but need partial pancreatectomy in severe cases (Glaser, 2010).
2. Beckwith-Wiedemann syndrome

**Typical scenario**: Up to the 3rd year of life. Hypoglycemia is seen in 50% of BWS patients, mostly asymptomatic/mild, but 20% of hypoglycemic episodes last > 1 week; associated with intellectual impairment. Other symptoms of BWS (macroglossia, macrosomia, omphalocele, umbilical hernia, ear pits, cancer.)

**Causes/Pathophysiology**: Unknown beta-cell abnormality leads to inappropriate insulin secretion.

**Treatment**: Glucose in mild cases. Diazoxide, cortisol, OR glucagon if necessary. Partial pancreatectomy in severe cases.

Review: (Munns and Batch, 2001).

3. Transient hyperinsulinism

**Typical scenario**: A subset of neonatal-onset persistent hyperinsulinaemic hypoglycaemia that spontaneously resolves. Risk factors are small for gestational age, asphyxiation at birth, and poor control of diabetes in the mother. May be seen in Beckwith-Wiedemann syndrome (above).

**Causes/Pathophysiology**: Varied. In infants of diabetic mothers, due to insulin hypersecretion as a response to hyperglycemia.

**Treatment**: Glucose IV, glucagon, diazoxide; must rule out other causes of congenital hyperinsulinism.

Review and atypical case report: (Yap et al., 2003).

4. Relative hyperinsulinism in treated diabetes mellitus

**Typical scenarios**:
1) Excess insulin: insulin overdose.
2) Poor PO intake +/- infection: oppositional behavior, gastroenteritis, sleep (fasting state).
3) Aerobic exercise for long durations.

May present asymptomatic when parents check blood glucose, with sudden onset of symptoms during daytime, or by unexpected death in bed (in type 1 diabetes: Sartor & Dahlquist, 1995). Associated with rebound hyperglycemia after glucose is given. Death from hypoglycemia is more common for pediatric diabetics (including adolescents) than for adults, but is still 10x less frequent than death from DKA (in type I diabetes: Edge et al., 1999; review of death in diabetes: Daneman, 2001.)

**Causes/Pathophysiology**: A common cause of hypoglycemia when diabetes is treated with insulin or insulin-raising drugs. The patient does not appropriately react to hypoglycemia due to the insulin, and also because diabetics do not have appropriate rises in plasma glucagon when hypoglycemic (shown in adults: Gerich et al., 1973). Common mechanisms are insulin overdose, too little food intake, or depletion of glucose by exercise.

**Treatment**: 
Mild hypoglycemia: 15 g glucose PO (Curtis and Hagerty, 2002). Post-exercise, 35-45 g glucose PO may be needed (Corigliano et al., 2006). In children with gastroenteritis or poor PO intake, possibly home treatment with smaller 20-150 microgram doses of glucagon SC, under phone guidance with rechecking of blood glucose (28 patient study: Haymond and Schreiner, 2001).

Moderate hypoglycemia: 15 g basic carbohydrates, then starch and proteins.

Severe hypoglycemia: ER visit and glucagon SC (0.5 mg under 10 years old, 1 mg over 10 years old: Curtis and Hagerty, 2002). Common side effect is vomiting.

ENDOCRINE DEFICIENCIES (KETOTIC)

**Typical scenario**: Hypoglycemia after a short fast. Child may have other symptoms of endocrine deficiencies such as hyperpigmentation, short stature, micropenis.

**Causes/Pathophysiology**: Adrenal insufficiency (Addison’s disease, secondary, tertiary), growth hormone deficiency, hypothyroidism.

**Treatment**: Manage glucose and correct the underlying disease.

ORGANIC ACIDEMIAS (KETOTIC AND NON-KETOTIC)

**Typical scenario**: Severe, acute onset, anion gap metabolic acidosis, ketosis, elevated lactate, neutropenia, thrombocytopenia. Hypoglycemia has been seen in methylmalonic acidemia and propionic aciduria (Worthen et al., 1994), with ketosis, acidosis, and neutropenia. Hypoglycemia with neither acidosis nor ketosis: HMG-CoA lyase deficiency (associated with Reye syndrome.) Acidosis without ketosis in biotin-unresponsive 3-methylcrotonyl-CoA carboxylase deficiency. Acidosis and ketosis also occur in other acidemias such as ketothiolase deficiency. (Enumerated in Middle Eastern population by Worthen et al., 1994).

**Causes/Pathophysiology**: Varied defects in branched-chain amino acid or lysine metabolism. Hypoglycemia is possibly due to inhibition of gluconeogenesis through various mechanisms: inhibition of malate shuttle by methylmalonic acid and inhibition of pyruvate carboxylase by methylmalonyl-CoA, inhibition of multiple enzymes by propionyl-CoA, and accumulation of organic acid CoA esters through acylcarnitine formation (Worthen et al., 1994).
Treatment: Depends on the particular disorder.
Review: (Seashore, 2009).

GLYCOGEN STORAGE DISORDERS (KETOTIC)
Often mild hypoglycemia with characteristic symptoms (massive hepatomegaly, growth retardation, hyperlipidemia, hyperuricemia, prolonged bleeding time.) Autosomal recessive diseases characterized by either a deficient or abnormally functioning enzyme involved in the formation or degradation of glycogen. Hypoglycemia is not typical in Type II (Pompe’s disease, defective alpha-glucosidase) because glycogenolysis is not impaired to clinically significant levels in the absence of the lysosomal hydrolase.
Review: (Heller et al., 2008).

GSD I:
Typical scenario: In newborns and in older infants. Neonatal: hypoglycemia with lactic acidosis. Older patients: hypoglycemia at night (fasting state), hepatomegaly, seizures. Other signs/symptoms: high triglycerides/cholesterol, lactate, uric acid; LFTs usually normal or slightly elevated; bleeding such as recurrent epistaxis; neutropenia with GSD Ib. Diagnosis by liver biopsy or genetics.
Causes/Pathophysiology: In GSD 1b, Neutrophil dysfunction and neutropenia due to dependence on membrane glucose transport/microsomal G6P transport.
Treatment: Frequent feeds sometimes including continuous nocturnal intragastric feeds to prevent night hypoglycemia, cornstarch therapy; avoid lactose, fructose, galactose; DDAVP for bleeding complications.

GSD III (Cori disease):
Typical scenario: Similar to type Ia but milder; liver symptoms (hepatomegaly, dyslipidemia) often resolve with puberty. Cardiac/skeletal myopathy in type IIIa (80% of cases) can start in childhood or much later than liver involvement. Short stature.
Causes/Pathophysiology: Defective glycogen debrancher leads to glycogen accumulation in liver in all cases; liver only in IIIb; liver + muscle in IIIa.
Treatment: Nutritional management with cornstarch as in GSD I but less strict.

GSD IV (Hers disease):
Typical scenario: Mild-moderate hypoglycemia, hepatomegaly and FTT in infants, sometimes slight liver enzyme, triglyceride and cholesterol elevation.
Causes/Pathophysiology: Glycogen phosphorylase deficiency specific to liver.
Treatment: High-carbohydrate, high-protein diet to prevent hypoglycemia.

DEFECTS IN GLUCONEOGENESIS AND SUGAR INTOLERANCE (NON-KETOTIC OR KETOTIC)

1. Fructose-1,6-diphosphatase deficiency
Typical scenario: Episodes of severe hypoglycemia and metabolic (lactic) acidosis triggered by ingestion of fructose or fasting. Hepatomegaly. Response to glucagon is intact. Patients can be ketogenic.
Causes/Pathophysiology: Both a gluconeogenesis defect under all conditions, and a glycogenolysis defect when fructose is ingested. The deficient enzyme, fructose-1,6-diphosphatase, catalyzes an essential step in gluconeogenesis, conversion of fructose-1,6-diphosphate to fructose-6-phosphate (which would be converted to G6P, then to glucose.) Since gluconeogenesis is defective, patients can have hypoglycemic episodes if glycogen stores are low (after fasting, or in newborns). Episodes are also triggered by ingestion of large amounts of fructose due to impairment of glycogenolysis: fructose-1-phosphate accumulation inhibits glycogen phosphorylase possibly by draining the ATP/phosphate pool, and metabolism of fructose-1-phosphate to lactate results in acidosis.
Treatment: Glucose IV and bicarbonate IV during hypoglycemia-acidosis episodes. Avoid fructose, sucrose, and sorbitol though patients can tolerate some amount of “sweet food.” Avoid fasting. Patients become able to tolerate fasting periods as they age. Review: (van den Berghe, 1996).

2. Fructose intolerance (aldolase B mutation)
Typical scenario: Intolerance to fructose, sucrose, and sorbitol. Often an infant who has received sweet food containing sucrose or fructose for the first time, and has nausea, bloating, and vomiting; lactic acidosis. Long term, hepatomegaly with liver damage and kidney damage.
Causes/Pathophysiology: Fructose-1-phosphate builds up, trapping phosphate and draining the ATP pool. Glycogenolysis is impaired since phosphate is necessary for glycogen phosphorylase. Fructose-1-phosphate also competitively inhibits phosphomannose isomerase, interfering with N-glycosylation.
Treatment: Control hypoglycemia and lactic acidosis as above for F-1,6-DP deficiency. Long-term strict avoidance of fructose, sucrose, and sorbitol.
### 3. Galactosemia

**Typical scenario**: Intolerance to lactose and galactose. Hepatomegaly, jaundice, cataracts, failure to thrive, sepsis (*E. coli*), diarrhea, vomiting, pseudotumor cerebri, mental retardation and renal Fanconi syndrome. Usually presents in first few days of life, or after milk exposure. Galactose-1-phosphate uridyl transferase deficiency is on most newborn screens.

**Causes/Pathophysiology**: Can be caused by galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) or by severe uridine diphosphate galactose 4-epimerase deficiency.

**Treatment**: Eliminate dietary galactose and lactose. Manage acute hypoglycemia as above. Give small amounts of galactose for patients with severe UDP-galactose-4-epimerase deficiency.

### 4. Other disorders

**PEP carboxykinase deficiency** is very rare; begins in neonatal period and involves FTT, microcephaly, developmental delay, seizures, hepatomegaly, renal tubular acidosis, cardiomyopathy and muscle weakness (van den Berghe, 1996).

**DEFECTS IN FATTY ACID METABOLISM (NON-KETOTIC)**

Abnormalities in fatty acid oxidation and ketone body formation result in nonketotic hypoglycemia triggered by periods of fasting or illness. Normally during fasting, free fatty acids would be mobilized from adipose tissue and oxidized directly by body tissue (heart, skeletal muscle, intestine) or undergo beta-oxidation in the liver with production and release of ketone bodies. Defects in carnitine transport, carnitine acyl transferase, long-, medium-, and short-chain acyl dehydrogenases, and carnitine deficiencies have been identified.

**There are multiple types:**

1. VLCAD (Very long-chain acyl CoA dehydrogenase deficiency)
2. LCAD (Long-chain acyl CoA dehydrogenase deficiency)
3. LCHAD (Long-chain L-3-hydroxyacyl CoA dehydrogenase deficiency)
4. SCAD (short-chain acyl CoA dehydrogenase deficiency)

**Presentation**: severe hypoglycemia, hypoketonemia, high plasma free fatty acid concentrations, hypotonia, hepatomegaly with microvesicular fat accumulation, elevated plasma activities of both liver and muscle enzymes, and frequently cerebral edema. May present with myopathy or cardiomyopathy and often the initial presentation is with a Reye-like episode.

**Evaluation**: includes measurement of carnitine levels [total, free and acylcarnitine (bound fraction), results are quantitative measurement of each fraction]. Acylcarnitine profile determines the nature of the carbon compounds bound to carnitine hence the acylcarnitine profile. Specific patterns on the profile give reliable information regarding the exact step that is defective in the FAO cycle. Urine organic acid analysis can detect dicarboxylic acids in times of metabolic derangement.

**SCHAD (Short-chain acyl CoA dehydrogenase deficiency)**
The defective enzyme is short chain L-3-hydroxyacyl-coenzyme A dehydrogenase. This is one of the congenital hyperinsulinemias (see above).

**MCAD (Medium-chain acyl CoA dehydrogenase deficiency)**

**Typical scenario**: Hypoketotic hypoglycemia triggered by fasting or illness, with vomiting, lethargy, hepatomegaly, seizures. Can present at any age though first acute episode is usually early (<2 years old). Also seen: myopathy, cardiomyopathy, sudden infant death syndrome, hyperammonemia, hyperuricemia, elevated creatine phosphokinase, dicarboxylic aciduria. ACADM mutation, commonly leading to K304E in the enzyme.

**Treatment**: IV glucose in acute episodes. Avoid fasting > 12 h in children; babies must be fed much more frequently. Cornstarch at bedtime. Avoid any infant formulas where the fat is mostly medium-chain triglycerides.

Review: (Matern & Rinaldo, 2005).

**ACUTE MANAGEMENT OF HYPOGLYCEMIA**

**Who to treat**: Plasma glucose <45 mg/dl with symptoms, or plasma glucose <25-35 mg/dl and asymptomatic.

**Treatment Options**: 1st line: IV glucose. Glucose is administered in a dose of 0.5 g/kg/dose. Dextrose 25 percent at a dose 2 to 4 mL/kg is appropriate. In neonates and preterm infants, dextrose 10 percent at a dose of 5 to 10 mL/kg/dose is used to avoid sudden hyperosmolarity. In older children and adolescents, dextrose 50 percent at a dose of 1 to 2 mL/kg/dose is used.
For hypoglycemia in known diabetic patients occurring outside the hospital, the child should receive glucose PO or an age-appropriate quickly absorbed source of calories, +/- glucagon SC and come to the hospital if symptoms are severe or glucose does not improve.

After an episode of hypoglycemia, glucose levels are monitored every 1 to 2 hours until the patient is alert and capable of eating and drinking.

**INFORMATION FOR PATIENTS**

Hypoglycemia in children, at [http://www.uchicagokidshospital.org/online-library/content=P01960](http://www.uchicagokidshospital.org/online-library/content=P01960)

**REFERENCES AND LINKS**


Back to Table of Contents