Not Your Typical Case of Ketotic Hypoglycemia

Linda Steinkrauss, RN, MSN, CPNP

Nemours. Alfred I. duPont Hospital for Children

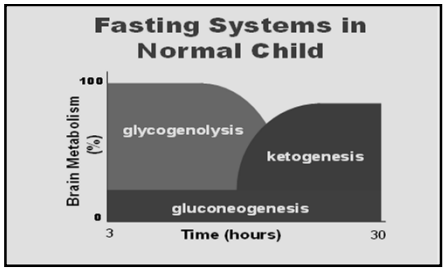
Objectives

By the end of this session, attendees should be able to:

1. **Discuss the difference between idiopathic ketotic hypoglycemia and an underlying disorder causing ketotic hypoglycemia.**
2. **Describe the process for evaluating ketotic hypoglycemia.**
3. **Explain the modes of genetic inheritance for certain disorders causing ketotic hypoglycemia.**

No conflicts of interest.

What is Ketotic Hypoglycemia(KH)?



Steinkrauss, LJ (2016). The path from hormone abnormality to hypoglycemia. *Journal of Pediatric Nursing*, 31(5), 562-564.

Normal Fasting Time

Newborn	12 Hours
Infant	24 Hours
Child	36 Hours
Adult	48+ Hours

Several Terms – Same Thing

- **Ketotic Hypoglycemia**
- **Idiopathic Ketotic Hypoglycemia**
- **Idiopathic Hypoglycemia of Childhood**

KH Typical Presentation

- **Young child with an illness**
  - **Vomiting and poor POs**
  - **Symptoms of hypoglycemia**
  - **ER – hypoglycemia and ketonuria**
  - **Often a one-time episode**

Repeated KH

- **Child characteristics**
  - **Thin**
  - **Poor eater**
  - **Fewer stores of fat and glycogen**
  - **Any illness or longer fast will cause ketosis and hypoglycemia**

KH Treatment and Prognosis

- **Well controlled with dietary changes**
  - **Limited fasting time**
  - **Mixed meals**
  - **Uncooked cornstarch (1-2 grams/kg)**
- **Typically resolves by school age**
- **Rarely causes seizures/brain damage**

Not all cases of ketotic hypoglycemia are of this typical variety.

Case Study

- **"Greg" is a 5 10/12 year old Caucasian boy with symptoms of hypoglycemia**
- **Symptoms**
  - **Always first thing in the morning**
  - **Irritability, abdominal pain, nausea, tachycardia, and frequently vomiting**
  - **Mom has noticed feeding him alleviates symptoms**

Case Study

- **Mild Symptoms Feed Resolve in 15 minutes**
- **Severe Symptoms Feed Last 4+ hours**
- **Fasts 11 hours overnight**
- **Eats a snack before bed of carbs/protein**

Past Medical History

- **Symptoms began at 2 years old**
- **Off and on for the past 3.5 years**
- **Normal cognitive and motor development**
- **No seizures**
- **No access to insulin, anti-diabetes medications, alcohol, or beta blockers**

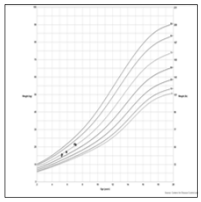
Family History

- **Maternal uncle and 2 distant maternal cousins (both boys) have had similar symptoms**
- **Uncle**
  - **Symptoms resolved by age 13**
  - **No intellectual disabilities nor obvious health problems**

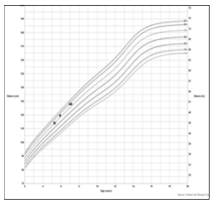
Greg's Physical Exam

- **No abnormalities**
- **No hepatomegaly**
- **Normal growth**

Growth Charts



Weight 75%ile



Height 75-90%ile

Evaluation

- **Home blood sugar and ketone monitoring**
- **Home → At time of symptoms**
  - **Hypoglycemia (BS=50s)**
  - **Ketonuria (Moderate to Large)**
- **Recommended a diagnostic fasting test**
- **Why?**

Time Lapse

…15 months later…
Now 7 years old

Insurance issues
Symptoms seemed better
Then symptoms returned

Evaluation

- **Inpatient diagnostic fasting test**
  - **11.5 hours with BS >70mg/dL**
  - **13.5 hours total**

Newborn	12 Hours
Infant	24 Hours
Child	36 Hours
Adult	48+ Hours

Diagnostic Fasting Lab Results

Component (reference range)	Result	Component (reference range)	Result
Glucose	49 mg/dL	Lactate (<2)	0.4 mmol/L
Insulin (<1)	<1.0 uIU/mL	C-peptide (<0.5)	0.1 ng/mL
BOHB (>2.5)	2.53 mM	Ammonia (0-33)	<9 umol/L
FFA (>2.5)	3.14 mM	Total Carnitine (35-84)	45 nmol/mL
Cortisol (>15)	17.6 mcg/dL	Free Carnitine (24-63)	20 nmol/mL
Growth Hormone (>10)	0.2 ng/ml*	Acylcarnitine profile and Urine Organic Acids	Normal

Results: Normal*

Additional Lab Results

Component	Reference Range	Result
TSH	(0.7-5.97)	1.88 uIU/mL
Free T4	(0.85-1.75)	1.71 ng/dL
IGF-1	(113-261)	165 ng/mL
IGFPB-3	(2.1-4.2)	4.0 mcg/mL
ALT	(10-25)	29 U/L
AST	(15-37)	28 U/L

Fasting Test Summary

- **Abbreviated fasting time for age**
- **No hyperinsulinism**
- **No fatty acid oxidation disorder**
- **Abbreviated fasting time + elevated liver enzyme + family history + age =**

not typical ketotic hypoglycemia

What Could It Be?

- **Genetic Disorders that cause ketotic hypoglycemia:**
  - **Glycogen Storage Disease 0 (Glycogen Synthase Deficiency)**
  - **Glycogen Storage Disease III (Debrancher Deficiency)**
  - **Glycogen Storage Disease VI (Phosphorylase Deficiency)**
  - **Glycogen Storage Disease IX (Phosyphorylase Kinase Deficiency)**
  - **Growth Hormone and/or Cortisol Deficiency**
  - **Other rare genetic disorders**

Growth Hormone/Cortisol Deficiency?

- **Normal cortisol level when hypoglycemic**
- **Normal growth**
- **Normal growth factors**
- **Normal thyroid function**

Very Unlikely

Glycogen Storage Disease?

- **Difficult to differentiate types**
- **Untreated GSDs typically associated with:**
  - **hepatomegaly**
  - **poor growth**
- **Greg did not have these**

What to do?

- **Confident not GH deficiency**
- **Some features of GSDs**
  - **KH**
  - **Mildly elevated liver enzyme**
- **Family history**

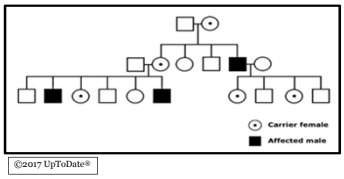
Genetic Evaluation

- **GSD NextGen Sequencing Panel (Prevention Genetics)**
  - **Screens for all types of GSD with one sample**
  - **Cheaper and quicker than testing 1 type of GSD at a time**
- **Newer Test – Metabolic Hypoglycemia NextGen Sequencing Panel**
  - **21 genes – all types of GSD plus other rare disorders that cause KH**

Genetic Results

- **+ for variant in PHKA2 - predicted to be disease causing**
- **PHKA2 is a gene that encodes phosphorylase kinase**
- **Located on the X chromosome**
- **This is an X-linked form of GSD IX**

Example of X-linked Inheritance



Family Testing

- **Maternal Uncle who also had symptoms has the same PHKA2 mutation**
- **Mom is an obligate carrier**
- **Sister could be a carrier – not yet tested**

Phosphorylase Kinase Deficiency

- **GSD IX**
- **Along with GSD VI (phosphorylase deficiency), account for 25% of all cases of GSD**

Wolfsdorf& Weinstein (2003). Glycogen storage diseases. *Reviews in Endocrine and Metabolic disorders*, 4: 95-102.

GSD IX – Clinical Features Variable

- **Ketotic hypoglycemia**
- **Growth retardation/short stature**
- **Weakness**
- **Fatigue**
- **Motor delay**
- **Hepatomegaly**
- **Mild hyperlipidemia**
- **Elevated liver enzymes**
- **Hepatic fibrosis and cirrhosis**
- **Hepatic adenomas**

Beauchamp et al. (2007). Glycogen storage disease type IX: high variability in clinical phenotype. *Mol Genet Metab*, 92(1-2): 88-99.
Tsilianidis et al. (2013). Aggressive therapy improves cirrhosis in glycogens storage disease type IX. *Mol Genet Metab*, 109(2): 179-182.

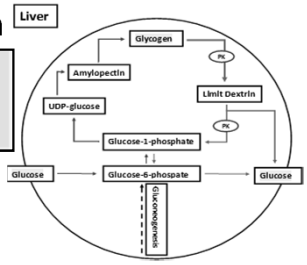
Phosphorylase Kinase (PK)

- **Present in Liver and Muscle**
- **4 subunits(α,β,γ,δ)**
- **3 different genes encode PK**
  - **PHKA2(α) – Liver only – X-linked – 75% of all cases**
  - **PHKB(β) – Liver and muscle – recessive inheritance**
  - **PHKG2(γ) – Liver only – recessive inheritance**
  - **No mutations identified in the δ subunit gene**

Wolfsdorf& Weinstein (2003). Glycogen storage diseases. *Reviews in Endocrine and Metabolic disorders*, 4: 95-102.
Tsilianidis et al. (2013). Aggressive therapy improves cirrhosis in glycogens storage disease type IX. *Mol Genet Metab*, 109(2): 179-182.

PK Action

Liver



Treatment

- **Uncooked cornstarch 0.6-2.5 grams/kg as needed to prevent ketogenesis**
  - **Ketones should remain <1mM/L**
- **High protein diet**
  - **2.5 gm/kg**
- **Avoid large quantities of simple sugars**
- **Limit fasting time**
- **Treatment lessens with age**

Goldstein et al. (2011). Phosphorylase kinase deficiency. *GeneReviews NIH*, 1-29.

Surveillance for GSD IX

- **Home BS and ketone measurement**
- **Yearly evaluation**
  - **Liver enzymes**
  - **Lipids**
  - **Growth parameters**
  - **Liver ultrasound**

Follow-up on Greg

- **High protein diet**
- **Avoid concentrated sugar**
- **Bedtime**
  - **Uncooked cornstarch ~1 gram/kg**
  - **Snack**
- **No further symptoms of hypoglycemia**
  - **FBSs normal and Ketones negative**

Summary

- **KH can be caused by an underlying genetic disorder**
- **Genetic testing warranted when KH associated with:**
  - **Short fasting time**
  - **Older child**
  - **Poor growth**
  - **Elevated liver enzymes**
  - **Hepatomegaly**

Questions?

- **Has anyone had cases of ketotic hypoglycemia that do not seem idiopathic?**
- **Have you had cases of a genetically identified cause for ketotic hypoglycemia?**

References

Beauchamp et al. (2007). Glycogen storage disease type IX: high variability in clinical phenotype. ***Mol Genet Metab,*** **92(1-2); 88-99.**

Goldstein et al. (2011). Phosphorylase kinase deficiency. ***GeneReviews NIH,*** **1-29.**

Steinkrauss, LJ (2016). The path from hormone abnormality to hypoglycemia. ***Journal of Pediatric Nursing,*** **31(5); 562-564.**

Tsilianidis et al. (2013). Aggressive therapy improves cirrhosis in glycogens storage disease type IX. ***Mol Genet Metab*****, 109(2); 179-182.**

Wolfsdorf & Weinstein (2003). Glycogen storage diseases. ***Reviews in Endocrine and Metabolic disorders*****, 4; 95-102.**