Metabolic disorders causing hypoglycemia

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Hypoglycemia

° 36w6/7, 3.6 kg day0: not feeding, pale, moaning: glc 22mg/dL
IV glc bolus, high glc need 16-18 mg/kg/min
Not possible to wean
Clin Ex: No hepatomegaly
Bloods: low FFA, no lactate, no urinary ketones
High insulin 36.5mIU/L
What is the diagnosis?

A. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
B. Fatty acid oxidation disorder
C. Glycogen storage disease (GSD)
D. Other
What is the diagnosis?

A. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI)
B. Fatty acid oxidation disorder
C. Glycogen storage disease (GSD)
D. Other
Isn’t it just hormonal?
<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Chromosome</th>
<th>Diazoxide responsive</th>
<th>Focal or diffuse</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABCC8, KCNJ11</strong></td>
<td>SUR1, KIR6.2</td>
<td>11p15</td>
<td>No</td>
<td>Diffuse</td>
<td>± protein sensitivity</td>
</tr>
<tr>
<td>Biallelic recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoallelic recessive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoallelic dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GLUD1</strong>, monoallelic dominant</td>
<td>GDH1</td>
<td>10q23.3</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Protein sensitivity, hyperammonemia</td>
</tr>
<tr>
<td><strong>GCK</strong>, monoallelic dominant</td>
<td>GK</td>
<td>7p15.3-p15.1</td>
<td>±</td>
<td>Diffuse</td>
<td>Hypoglycemia typically mild</td>
</tr>
<tr>
<td><strong>HADH</strong>, biallelic recessive</td>
<td>SCHAD</td>
<td>4q22-q26</td>
<td></td>
<td>Diffuse</td>
<td>Protein sensitivity, abnormal acylcarnitine profile</td>
</tr>
<tr>
<td><strong>SLC16A1</strong>, monoallelic dominant</td>
<td>MCT1</td>
<td>1p12</td>
<td>±</td>
<td>Diffuse</td>
<td>Commonly exercise-induced hypoglycemia</td>
</tr>
<tr>
<td><strong>UCP2</strong>, monoallelic dominant</td>
<td>UCP2</td>
<td>11q13</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Transient HI resolves by 6 months to 6 years</td>
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<tr>
<td><strong>HNF1A</strong>, monoallelic dominant</td>
<td>HNF1α</td>
<td>12q24.2</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Transient HI resolves by 6 years, later development of MODY3</td>
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<tr>
<td><strong>HNF4A</strong>, monoallelic dominant</td>
<td>HNF4α</td>
<td>20q13.12</td>
<td>Yes</td>
<td>Diffuse</td>
<td>Transient HI resolves by 4 years, later development of MODY1</td>
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</tbody>
</table>
Glucose is fuel

Glucose → energy, work → food → glucose
Hypoglycemia
HYPO

Wisselend humeur

Hoofdpijn

Moeheid

Bleekheid

Honger

Zweten

Beven

Slecht zien

Duizeligheid
Why do we need glucose?

Basal glucose oxidation rate

- Neonate: 4–6 mg/kg/min
- Infants & children: 3–5 mg/kg/min

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Brain</th>
<th>Muscle</th>
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<tbody>
<tr>
<td>3m</td>
<td>5.5</td>
<td>0.65</td>
<td>1.21</td>
</tr>
<tr>
<td>18 m</td>
<td>11</td>
<td>1.05</td>
<td>2.57</td>
</tr>
<tr>
<td>5 years</td>
<td>19</td>
<td>1.24</td>
<td>6.65</td>
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<tr>
<td>10 years</td>
<td>31</td>
<td>1.35</td>
<td>11.60</td>
</tr>
<tr>
<td>14 years</td>
<td>50</td>
<td>1.36</td>
<td>21</td>
</tr>
<tr>
<td>Adult</td>
<td>70</td>
<td>1.40</td>
<td>28</td>
</tr>
</tbody>
</table>
Hypoglycemia can be due to many reasons

Chemical / poisoning
- 1,1-Dichloroethene, Ackee fruit, Jamaican vomiting sickness, Systemic monochloroacetate poisoning

Drug Side Effect
- Acetohexamide, Amprenavir, Chloramphenicol, Chlorpromazine, Chlorpropamide, Cibenzoline, Clove, Ethanol, Ethionamide, Fluorodeoxyglucose, Gatifloxacin, Ginseng, Gilbenclamide, Glialazine, Glimepiride, Glipizide, Glitazone, Glisoxepide, Insulin, Insulin-like growth factor, Lanreotide, Levomepromazine, Mitiglinide, Nateglinide, Pazopanib, Pentamide, Perazine, Pipothiazine, Pramlintide, Quinine, Repaglinide, Rivatan, Saquinavir, Somatostatin, Sulfamethoxazole, Temafloxacin, Tolazamide, Tolbutamide, Trimethoprim

Endocrine Addison's disease, Adrenal cortex insufficiency, Adrenal insufficiency, Beginning stages of diabetes, Glucagon deficiency, Hypopituitarism, Hypothyroidism, Multiple endocrine neoplasia, Myxedema coma, Timme syndrome

Gastroenterologic
- Acute fatty liver of pregnancy, Acute liver failure, Cirrhosis, Diabetic gastroparesis, Diarrhea, Dumping syndrome, Functioning pancreatic endocrine tumor, Gastric dumping syndrome, Hepatic congestion, Hepatic failure, Idiopathic postprandial syndrome, Insulinoma, Liver cancer, Malabsorption, Maldigestion, Reactive hypoglycemia, Severe hepatitis

Genetic
- 2-methylbutyryl-coenzyme A dehydrogenase deficiency, 3-alpha-hydroxacyl-CoA dehydrogenase deficiency, 3-Methylcrotonyl-CoA carboxylase deficiency, ACAD9 deficiency, Alpers' syndrome, Carbohydrate-deficient glycoprotein syndrome type 1b, Carnitine palmitoyltransferase 1 deficiency, Carnitine-acylcarnitine translocase deficiency, Cleft lip palate pituitary deficiency, Dicarboxylicaminocarboxiurias, Dihydroxiopamide dehydrogenase deficiency, Donohue syndrome, Dopamine beta-hydroxylase deficiency, Familial glucocorticoid deficiency, Familial hyperinsulinemic hypoglycemia type 3, Familial hyperinsulinemic hypoglycemia type 5, Familial hyperinsulinemic hypoglycemia type 7, Fructose-1,6-diphosphatase deficiency, Fructose-1-phosphate aldolase deficiency, Galactose-1-phosphate uridylytransferase deficiency, Glucose 6-phosphate dehydrogenase deficiency, Glutaric acidemia type 2, Glycogenosis type 1a, Glycogenosis type 1b, Glycogenosis type 3, Glycogenosis type 6, Glycogenosis type 9a, Glycogenosis type 9b, Glycogenosis type 9c, Glycogenosis type V, Growth hormone deficiency (congenital, Hereditary ACTH resistance, HMG-CoA lyase deficiency, Hydroxymethylglutaryl-CoA lyase deficiency, Hyperinsulinism-hyperammonemia syndrome, Laron dwarfism, Leucine-induced hypoglycemia, Liver glycogen synthase deficiency, Long-chain hydroxyacyl-CoA dehydrogenase deficiency, Malonyl-CoA decarboxylase deficiency, Maple syrup urine disease, Medium chain acyl-CoA dehydrogenase deficiency, Methylmalonic acidemia, Mitochondrial DNA depletion syndrome, hepatocerebral form, Mitochondrial trifunctional protein deficiency, Navajo neurohepatopathy, Nephroblastomatosis-fetal ascites-macrosomia-wilms tumor, Nesioblastosis, Plasma membrane carnitine transporter deficiency, Propionyl-CoA carboxylase deficiency, PCCA type, Short-chain acyl-CoA dehydrogenase deficiency, Short stature-pituitary and cerebellar defects-small sella turcica, Triple A syndrome, Tyrosinaemia type 1, Very-long-chain acyl-CoA dehydrogenase deficiency, Wiedemann-Beckwith syndrome, X-linked congenital adrenal hypoplasia

Hematologic
- Hemolytic disease of the newborn

Iatrogenic
- Gastrojejunostomy, Postgastrectomy syndrome, Pyloroplasty, Rye syndrome

Infectious Disease
- Acute meningitis, Malaria (malignant tertian), Sepsis, Visceral leishmaniasis

Neurologic
- Acute fatty liver of pregnancy, Malignant tertian, Sepsis, Visceral leishmaniasis

Nutritional / Metabolic
- Coenzyme Q cytochrome c reductase deficiency, Deficiency in enzymes of fat oxidation, Fructose intolerance, Galactosemia, Glucose-6-phosphate dehydrogenase deficiency, Inborn error of metabolism, Methylmalonic acidemia, Mitochondrial trifunctional protein deficiency, Navajo neurohepatopathy, Nephroblastomatosis-fetal ascites-macrosomia-wilms tumor, Nesioblastosis, Plasma membrane carnitine transporter deficiency, Propionyl-CoA carboxylase deficiency, PCCA type, Short-chain acyl-CoA dehydrogenase deficiency, Short stature-pituitary and cerebellar defects-small sella turcica, Triple A syndrome, Tyrosinaemia type 1, Very-long-chain acyl-CoA dehydrogenase deficiency, Wiedemann-Beckwith syndrome, X-linked congenital adrenal hypoplasia

Obstetric/Gynecologic
- Diabetic mother, Gestational diabetes, Intrauterine growth retardation, Pregnancy, Premature labour and/or delivery, Sheehan syndrome

Oncologic
- Adrenal cancer, Doege-Potter syndrome, IGF producing tumors, Tumors, Functioning pancreatic endocrine tumor, Insulinoma, Liver cancer, Mesothelioma

Overdose / Toxicity
- Acetohexamide, Amprenavir, Chloramphenicol, Chlorpromazine, Chlorpropamide, Cibenzoline, Clove, Ethanol, Ethionamide, Fluorodeoxyglucose, Gatifloxacin, Ginseng, Gilbenclamide, Glcialazine, Glimepiride, Glipizide, Gliquidone, Glisoxepide, Insulin, Lanreotide, Levomepromazine, Mitiglinide, Nateglinide, Pazopanib, Pentamide, Perazine, Pipothiazine, Pramlintide, Quinine, Repaglinide, Rivatan, Saquinavir, Somatostatin, Sulfamethoxazole, Temafloxacin, Tolazamide, Tolbutamide, Trimethoprim

Psychiatric
- Anorexia nervosa, Bulimia nervosa, Munchausen syndrome

Pulmonary
- Mesothelioma

Renal / Electrolyte
- Benign glaucosia, Renal Hypoplasia, Renal failure

Rheum / Immune / Allergy
- Autoimmune adrenitis, Hemolytic disease of the newborn, Immunopathologic hypoglycemia, Insulin receptor antibodies

Trauma
- Burns

Miscellaneous
- Alcoholism, Binge drinking, Cachexia, Delayed separation blood sample, Drip arm sample, Fasting, Heavy exercise, Hypothermia, Idiopathic hypoglycemia, Septic shock, Starvation (acute)
Putting it all together....

- According to its timing

- Permanent: PHHI, factitious
- Post-prandial: HFI, Gal, PHHI
- Fasting: PHHI

Short fasting: GSDI
Long fasting: FBP, FAO

Timing?
Hepatomegaly?
Lactate?
Ketones?
Phase 1: Post-prandial <2.5 hours after meal
- Hyperinsulinism
- Hereditary fructose intolerance

Phase 2: Short fast >2.5 hours to <12 hours after meal
- Glycogenosis
- Glycogen synthase defect
- Gluconeogenesis defects

Phase 3: Medium to long fast >12 hours after meal
- Gluconeogenesis defects
- Mostly fatty acid oxidation defects with hypoketosis
- Ketotic hypoglycemia with major ketosis
Putting it all together….

- Hepatomegaly?

Permanent
PHHI, factitious

Post-prandial
HFI, Gal, PHHI

Fasting

Short fasting: GSDI
Long fasting: FBP, FAO

Timing?
Hepatomegaly?
Lactate?
Ketones?
Putting it all together....

- Hepatomegaly ?

- **Permanent**
  - PHHI, factitious

- **Post-prandial**
  - HFI, Gal, PHHI

- **Fasting**
  - Hepatomegaly
  - No hepatomegaly

Short fasting: GSDI
Long fasting: FBP, FAO

Timing ?
Hepatomegaly ?
Lactate ?
Ketones ?
Putting it all together...

- Lactate?

Permanent
- PHHI, factitious

Post-prandial
- HFI, Gal, PHHI

Fasting
- Hepatomegaly
- No hepatomegaly

- Ketonemia
- No ketonemia

Timing?
- Hepatomegaly?
- Lactate?
- Ketones?
Putting it all together...

- Ketonuria?

Permanent:
- PHHI, factitious

Post-prandial:
- HFI, Gal, PHHI

Fasting:
- Hepatomegaly
- No hepatomegaly

Hepatomegaly:
- Postprandial lactate
  - GSD III, VI, IX
- Fasting lactate
  - Short fasting: GSDI
  - Long fasting: FBP, FAO
- Ketones
  - Ketotic Hypoglc
  - Ketolysis
- no ketones
  - FAO
  - Ketogenesis
  - PHHI

Timing?
Hepatomegaly?
Lactate?
Ketones?
Putting it all together....

- Hypoglycemia samples
- Glucose
- Lactate
- Insulin + cortisol
- ACARP
- Urine Ketones + Organic acids

- (FFA, BHB = 2 ml heparin + freeze)
Case: Hypoglycemia

° 38w4/7, day0: glc 14mg/dL after 10h, over the following weeks repeatedly glc 30 mg/dL despite 3-hourly feeding.

Seizures with hypoglycemia R/ luminal
Clin Ex(6w): 4.5kg, normal tone, Epicanthic fold, prominent cheeks, Soft liver 2-3 cm BCM
Bloods: Low insulin during hypo, normal cortisol, normal PAA, ACARP, UOA, no ketonuria, initially ↑lactate, Bic 15 (at time of hypoglycemia)
Permanent Post-prandial Fasting

PHHI, factitious

Postprandial lactate

HFI, Gal, PHHI

Fasting lactate

Hepatomegaly

No hepatomegaly

Ketones

no ketones

GSD III, VI, IX

Short fasting: GSDI

Long fasting: FBP, FAO

Ketotic Hypoglycemias

Ketolysis

FAO

Ketogenesis PHHI
Lactic acidosis in GSD type Ia
Glycogen storage disease type I. Liver biopsy showing mosaic pattern, prominent cell membranes and rare nuclear hyperglycogenation (HE stain)
Hypoglycemia

1y-old, vomiting after fruit mix, no appetite, went to sleep
Morning: Twitching of the arms
Hypoglycemia 4mg/dL
Clin Ex: Seizures, liver 1 cm
Bloods: hypogluc, No ketones, Appropriately low insulin, Dicarboxyluria, elevated FFA
Permanent

PHHI, factitious

Post-prandial

HFI, Gal, PHHI

Hepatomegaly

Fasting lactate

Ketones

no ketones

Fasting

Hepatomegaly

No hepatomegaly

Postprandial lactate

Short fasting: GSDI

Long fasting: FBP, FAO

Ketotic Hypoglyc

Ketolysis

FAO

GSD III, VI, IX
1st step = length specific!

SCAD: 4 - 6C
MCAD: 6 – 10C
VLCAD: 12 – 18C
Acylcarnitine Analysis

MCAD Deficiency

Intensity

C₂
C₆
C₈
C₁₀:1
C₁₆

m/z, amu

Control

Intensity

C₂

m/z, amu

*: internal standards
Hypoglycemia & acidosis

2y-old, Vomiting and diarrhea, Evolution to somnolence

Bloods: pH 6.95, bic 3.3mmol/l, pCO2 16mm Hg; No lactate, ketones ++ in urine, no glucosuria, hypoglycemina at admission
Permanent

Post-prandial

- HFI, Gal, PHHI

Fasting

Hepatomegaly

- No hepatomegaly

Ketones

- no ketones

Postprandial lactate

Fasting lactate

Ketotic Hypoglycemia

Ketolysis

FAO

GSD III, VI, IX

Short fasting: GSDI

Long fasting: FBP, FAO

PHHI, factitious

1

2

3

4

5
Ketones are alternative fuel
Hypoglycemia?

A 9 year old male is brought to the emergency room due to vomiting and lethargy shortly after a birthday party. (glc 40mg/dL)

PMHx is significant for FTT in late infancy which resolved without determination of a diagnosis. He had had several bouts of vomiting in the past, usually after consuming candy or soft drinks. Labs reveal elevated AST and ALT.
Permanent

HFI, Gal, PHHI

Post-prandial lactate

Post-prandial

GSD III, VI, IX

Short fasting: GSDI

Long fasting: FBP, FAO

1

Hepatomegaly

Fasting lactate

Ketones

Ketotic Hypoglc

Ketolysis

Fasting

No hepatomegaly

no ketones

FAO Ketonogenesis PHHI

2

3

4

5
Take home:

Permanent: PHHI, factitious
Post-prandial: HFI, Gal, PHHI
Fasting: Hepatomegaly, No hepatomegaly

Postprandial lactate: GSD III, VI, IX
Fasting lactate: Short fasting: GSDI
Long fasting: FBP, FAO
Ketones: Ketotic Hypoglc
Ketolysis: FAO
Ketogenesis: PHHI

Timing?
Hepatomegaly?
Lactate?
Ketones?
Or more easy to remember

- Hypoglycemia + Hepatomegaly = GSD
- Hypoglycemia + high Insulin = PHHI
- Hypoglycemia – ketones = PHHI or FAO
  » Measure insulin
- Postprandial hypoglycemia = HFI
- High ketones and acidosis = ketone metabolism
- Consider central hypo = GLUT1
These samples are your friends

- Glucose
- Lactate
- Insulin + cortisol
- ACARP
- Urine Ketones + Organic acids
- (FFA, BHB = 2 ml heparin + freeze)
These samples are your friends
Dank voor jullie aandacht!