Hypoglycaemia

Endocrinology for FRACP
Michele O’Connell

Overview
- Normal Physiology – adaptation to fasting
- Clinical features
- Aetiology
- Evaluation and management

Normal perinatal physiology
- Transition from environment with continuous source of glucose (maternal blood) to one where glucose is in limited and intermittent supply!
- Glucose is preferred substrate for brain metabolism, which uses most of the 5-8mcg/kg/min produced and used by full-term neonate
- Glucose entry into brain cells is dependent on circulating arterial glucose concentration

Fasting adaptation
- Elaborate defense mechanism against hypoglycaemia
- Several metabolic systems act to maintain normoglycaemia during fasting
  - Integrated by ANS and hormones
  - Act synergistically to enhance glucose production while simultaneously limiting peripheral glucose use
- Hypoglycaemia results from:
  - A failure one of these fasting systems, or
  - An abnormality in a hormone that controls these systems

Mechanisms of fasting adaptation

Hormonal control of fasting
- GLUCAGON stimulates glycogenolysis and to lesser extent gluconeogenesis & ketogenesis
- GH stimulates lipolysis
- CORTISOL stimulates gluconeogenesis (and lipolysis)
- EPINEPHRINE stimulates glycogenolysis, gluconeogenesis, lipolysis and ketogenesis
- INSULIN inhibits / suppresses all of the fasting systems
Defects in glycogenolysis – glycogen storage disease (GSD)

Defects in gluconeogenesis (GNG)

Fatty acid oxidation disorders and defects in ketogenesis

Counterregulatory hormone abnormalities

Symptoms and signs of hypoglycaemia

<table>
<thead>
<tr>
<th>Plasma Glucose</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.9 mmol/l</td>
<td>Counterregulation</td>
</tr>
<tr>
<td></td>
<td>Glucose, epinephrine, norepinephrine, growth hormone</td>
</tr>
<tr>
<td></td>
<td>(3.6 &amp; 3.8 mmol/l), cortisol (0.1 mmol/l)</td>
</tr>
<tr>
<td></td>
<td>glycogen breakdown &amp; gluconeogenesis</td>
</tr>
<tr>
<td>3.3 mmol/l</td>
<td>Autonomic symptoms</td>
</tr>
<tr>
<td></td>
<td>Nausea, vomiting, hypotension, tachycardia, diaphoresis</td>
</tr>
<tr>
<td>2.6 mmol/l</td>
<td>Neuroglycopenic symptoms</td>
</tr>
<tr>
<td></td>
<td>Fatigue, hunger, dizziness, visual symptoms, inappropriate behaviour, focal neurologic symptoms</td>
</tr>
<tr>
<td>2.2 mmol/l</td>
<td>Lethargy</td>
</tr>
<tr>
<td>1.7 mmol/l</td>
<td>Coma</td>
</tr>
<tr>
<td>0.6 mmol/l</td>
<td>Convulsions</td>
</tr>
<tr>
<td>&lt;0.8 mmol/l</td>
<td>Permanent damage/death</td>
</tr>
</tbody>
</table>
**Pointers to diagnosis**

**Neonatal**
- Jitteriness
- Lethargy, poor feeding
- Seizures
- Hypothermia
- Resp distress / Apnoea

**Postnatal**
- Headache
- Irritability
- Syncope / collapse
- Confusion
- Seizures

**Definition of hypoglycaemia**
- Blood glucose level <2.6mmol/l
- Symptoms of hypoglycaemia
- Resolution of symptoms with treatment to raise BGL

Capillary glucometer readings are unreliable at low readings. Confirm with true lab glucose before ‘critical sample’

**Aetiology**

**Transient neonatal hypoglycaemia**
- Normal newborn – developmental immaturity
- Hyperinsulinism due to maternal factors – eg DM, iv glucose in labour

**Persistent hypoglycaemia**
- Neonatal
- Infancy or childhood

**Common age-related presentations**

**Neonatal**
- Preterm
- SGA
- Infant of diabetic mum
- Hyperinsulinism
- Hypopituitarism

**Postnatal and beyond...**
- Hyperinsulinism
- GSD
- Ketotic hypoglycaemia
- Hypopituitarism

The shorter the fasting interval before hypoglycaemia manifests, the more severe the defect
Hyperinsulinism

- Important to recognise
- Insulin suppresses all mechanisms of fuel generation
  - ↓glucose, ↓gluconeogenesis, ↓FAO & ↓ketogenesis
- Unique combination of hypoglycaemia + suppression of ketogenesis
  - → no fuel source for brain
- ANY detectable insulin (>2 microU/ml) in the presence of a BGL <2.6 mmol/l is inappropriate
- Aim of treatment is BGL >4.0 mmol/l

Insulin secretion - mechanism

- The beta cell functions to transform the chemical energy of glucose metabolism (ATP) to electrical energy that governs insulin secretion by way of voltage-gated calcium channels
- Process regulated by $K_{ATP}$ channels, which consist of an inward rectifying channel of the Kir6.2 family and its regulatory subunit, the sulphonylurea receptor SUR1.

Persistent Hyperinsulinaemic Hypoglycaemia of Infancy (PHHI)

- Clinically and genetically heterogeneous disorders which result in dysregulated insulin secretion and severe and persistent hypoglycaemia
- Can be caused by alterations in the structural, functional, or regulatory components of the KATP channel
- These alterations include:
  - mutations in SUR1
  - mutations in Kir6.2
  - Glutamate dehydrogenase gene mutations
  - Glucokinase gene mutations
- Also associated with:
  - SCHAD deficiency (exceptionally rare)
  - Congenital disorders of glycolysis

$K_{ATP}$ channel HI

- Loss of function mutations in either Kir6.2 or SUR1 subunits
- Most common and most severe form of PHHI
- >100 known mutations in gene for SUR1 (ABCC8); ~20 in gene for Kir6.2 (KCNJ11)
  - Can be AR, AD or sporadic
  - AR inheritance forms tend to be more severe
Histologic forms of sporadic K<sub>ATP</sub> -HI

- **Focal (40-60%)**
  - Distinct nodular proliferation of tissue within an otherwise normal pancreas
  - "Double hit" mechanism
    - i) loss of maternal allele in p15 region of Chr11
    - ii) mutation in the paternal allele, that is now unbalanced by normal maternal allele
  - Somatic reduction to hemizygosity, or homozygosity for mutated paternal allele in a portion of beta cells
  - focal abnormal lesion
- **Diffuse**
  - Beta cells throughout the pancreas are abnormal
  - Much more difficult to manage

Glutamate dehydrogenase HI

- 2<sup>nd</sup> most common HI
- Gain of function mutation of GDH
  - Key regulator of amino acid and NH₃ metabolism in pancreatic beta cells, liver and brain
- "Hyperinsulinism & hyperammonaemia syndrome"
- GDH is normally activated by leucine
  - Leucine sensitivity is a hallmark (protein meal)
  - Fasting and postprandial hypoglycaemia
- Usually less severe than K<sub>ATP</sub>-HI
  - Often present at few months of age
  - NH₃ usually x2-3 normal; asymptomatic

Glucokinase HI

- Activating mutations in GCK which encodes glucokinase
- Increased affinity of glucokinase for glucose, leads to dysregulated insulin production

Pointers to HI

- Macrosomic baby (or SGA / asphyxia)
- Early onset hypoglycaemia – often severe, recurrent
- Glucose requirement usually >10mg/kg/min
- Glycaemic response to glucagon

Investigations:
- Detectable insulin at hypoglycaemia
- Absence of ketones (bld and urine)
- Inappropriately low FFA
Counter-regulatory hormone defects

- Deficiencies of ACTH / cortisol or GH
- Hypoglycaemia in GHD is due to decreased lipolysis (and glycogenolysis to lesser extent)
- In ACTH/ cortisol deficiency, hypoglycaemia results from increased insulin sensitivity, decreased gluconeogenesis and increased glucose oxidation

Defects in glycogenolysis

- Glycogen storage disorders (GSD) due to AR mutations in genes involved in glycogenolysis
- Hepatomegaly (soft, often massive)
- Hypoglycaemia with fasting
  - Usually present in later infancy as inter-feed interval increases, or during intercurrent illness
- Lipolysis and ketogenesis intact
  - Less symptomatic than HI as alternate fuel available
  - Increased TG and ketone levels

GSD

- GSD 1a – impairment of both glycogenolysis and GNG; early hypoglycaemia can occur
  - GNG defect causes lactic acidosis
  - Completely dependent on exogenous glucose
  - Kidney involvement; RTA, microalbuminuria
- GSD III
  - Muscle weakness, cardiomyopathy, hypotonia
- GSD VI and IX – milder phenotypes
- GSD 0: defect in glycogen synthesis
  - Fasting hypoglycaemia and postprandial hyperglycaemia
  - CHO – lipolysis in liver – elevated lactate

Defects of gluconeogenesis

- Fructose 1,6-diphosphatase deficiency
- Phosphoenolpyruvate carboxykinase (PEPCK) deficiency
- Pyruvate kinase deficiency

- Features:
  - Glycogenolysis remains intact
  - Later onset; hypoglycaemia occurs in setting of fasting or intercurrent illness
  - Positive glucagon response in the fed but not fasted state
  - Keto- and lactic acidosis; hyperuricemia, hyperlipidemia
  - Hepatomegaly (lipid as opposed to glycogen storage)
Fatty acid oxidation defects

- Errors in pathway of: fatty acid uptake & activation and mitochondrial oxidation
- Defects in:
  - Carnitine synthesis, CPT1 and 2 (transporters)
  - Acetyl-CoA dehydrogenase – SCAD, MCAD, LCAD
  - HMG-CoA lyase (3 hydroxy-3-methylglutaryl-CoA) lyase
- Delayed onset (after infancy)
- Phenotype varies according to level of mutation
- Often unmasked by fasting / intercurrent illness
- Skeletal and cardiac muscle and liver – target organs

Features of FAO defects

- Clinical:
  - Myopathy, cardiomyopathy
  - Encephalopathy (Reye's syndrome)
  - Hepatic failure
- Laboratory:
  - Low or absent ketones
  - Diagnosis – urinary organic acids, carnitine profiles

Rarer causes...

Galactosemia (GALT def)

- Clinical features:
  - Neonatal onset
  - Neonatal hypoglycaemia
  - Neonatal cholestasis, diarrhea
- Lab features:
  - Non-ketotic
  - Urine reducing substance +
  - Increased Galactose-1-P
  - Low Galactose-1-phosphate uridyl transferase (GALT) level

Hereditary Fructose Intolerance

- Clinical features:
  - Onset after weaning
  - Deficiency of fructose-1-phosphate aldolase (inhibits hepatic GNG)
  - RTA, cholestasis, failure to thrive
- Lab features:
  - Non-ketotic
  - Urine reducing substance +
  - Hypo after fructose load

Accelerated starvation

- Previously / often referred to as 'ketotic hypoglycaemia', but preferable not to use that term
- Commonest cause of hypoglycaemia beyond infancy
  - Impaired fasting adaptation
- Clinical Features:
  - Often lean child
  - Early morning hypoglycaemia
  - Hypoglycaemia following prolonged fast (e.g. intercurrent illness)
  - Usually onset age 2-5 years; resolves by 10 years
  - Diagnosis of exclusion

Evaluation and Management

- See additional slides for clinical history etc
Investigations - Indications
- Neonatal
  - Persistent beyond first week
  - GIR > 12 mg/dL
- No risk factor (DM, NIE, GCA)
- Post-neonatal - Persistent

Critical samples
- Urine - Ketone, RS, organic/amino acid
- Blood
  - Sodium, potassium, ammonia
  - Bicarbonate, lactate, ketones
  - GH, insulin, cortisol, C peptide
  - Fatty acids, carnitine, organic acid

Controlled fast: parameters studied
- Glucose, lactate
- Free fatty acids, Ketones
- Amino acid profile
- Organic acids
- Ammonia
- TCO2
- Hormones - Insulin, cortisol, growth hormone

Controlled fast: duration
<table>
<thead>
<tr>
<th>AGE</th>
<th>&lt;6 mo</th>
<th>6-12 mo</th>
<th>1-2 yr</th>
<th>3-7 yr</th>
<th>&gt;7 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION</td>
<td>6 hr</td>
<td>12 hr</td>
<td>16 hr</td>
<td>16 hr</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

Ketone
- Low, absent
  - FAO defect
  - Hyperinsulinism
  - Galactosemia
  - Fructose intolerance
- Present
  - GSD
  - GNG defect
  - Ketotic Hypoglycemia
  - Hypopituitarism

Lactate
- High
  - GSD I
  - GNG defect
- Normal
  - Hyperinsulinism
  - Hypopituitarism
  - GSD III, VI
  - FAO defect
Confirmatory tests
- Hyperinsulinism work-up
- Liver biopsy
- Metabolic screen
- Hypoglycaemia - MRI head, TFT, U&Es

Hypocrinsulinism with hypoglycaemia
- Any detectable insulin
- Inappropriate glucagon response
- Markers of increased insulin action
  - Suppressed free fatty acids (< 1.5 mmol/L)
  - Low beta-hydroxybutyrate (< 2 mmol/L)

Investigations
- Maternal blood glucose, Hba1c
- Genetic study (DW0, KATP, GDI1, GCK)
- Ammonia (high in GDH mutation)
- Localization study - DOPA PET scan

Acute
- Dextrose bolus - 200 mg/kg (2 ml/kg of 10% Dx)
- Dextrose Infusion - GIV- 0 mg/kg/min
- Maintain BG > 3.3 mmol/L (minimum - preferably >4.0mmol/L)
- Increase GIV by 2 mg/kg/min if low BS

Hyperinsulinism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazoxide</td>
<td>High</td>
<td>First line</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Moderate</td>
<td>Short term</td>
</tr>
<tr>
<td>Glucagon</td>
<td>High</td>
<td>Short term</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Moderate</td>
<td>Second line</td>
</tr>
</tbody>
</table>
Surgery
- Indications
  - Diffuse form unresponsive to diazoxide
  - Focal lesion
- Procedures
  - Diffuse - Sub-total pancreatectomy (95%)
  - Focal - Focal resection

Specific management
- GSD/ Gluconeogenic defect
  - Continuous NG feed, corn starch
  - Allopurinol (GSD I)
- Hypopituitarism - GH, cortisol
- FAO defect - Avoid fasting, carnitine

Specific management
- Ketotic hypoglycaemia
  - Nocturnal feeds
  - Illness - Ketone, increased CHO intake
  - Protein crash, ketona monitoring
- Galactosemia/ FI - Dietary changes

Key practice points
- Any child with unexplained hypoglycaemia should be investigated
- Most useful investigations during presenting episode
- If no diagnosis established on baseline investigations controlled fast necessary
- Controlled fast – important to exclude disorders and to establish normal fasting responses

Additional slides...
Aetiology

Decreased stores:
- Ketotic hypoglycaemia / 'accelerated starvation'
- GSD/GNG defect
- Galactosaemia
- Fructose intolerance

Increased utilisation:
- Hyperinsulinism
- FAO defect
- Septicaemia / stress

Increased utilisation:
- FAO defect
- Septicaemia / stress
- Fructose intolerance

Fasting adaptations

<table>
<thead>
<tr>
<th>Level</th>
<th>Mediator</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Diet</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>Glucose</td>
<td>10-12 hr</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>Cortisol</td>
<td>12-24 hr</td>
</tr>
<tr>
<td>Lipolysis</td>
<td>GH</td>
<td>17-36 hr</td>
</tr>
</tbody>
</table>

Neonatal history

- Gestation, birth weight
- Birth asphyxia, sepsisemia, IDM
- Glucose requirement
  - 6.8 mg/kg/minute: Substrate defect
  - > 12 mg/kg/minute: Hyperinsulinism

Neonatal examination

- Large for date - Hyperinsulinism
- Microphimosis, mid line defect - Hypopituitaryism
- Genital ambiguity, pigmentation - CAH
- Blindness - Septo-optic dysplasia

Post-neonatal history

- Hypotonia (FAO, GSD)
- Recurrent cnoephlopathy (FAO)
- Jaundice (GSD III, FAO, galactosemia)
- Family history (GSD, FAO, MEN I)

Post-neonatal examination

- Hepatomegaly - GSD, GNG defct
- Renomegery - GSD I
- Myopathy - (GSD), FAO defect
- Pigmentation - Adrenal insufficiency
Most common causes by age:

<table>
<thead>
<tr>
<th>Onset</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Hyperinsulinism, OHID, GALT</td>
</tr>
<tr>
<td>Infant</td>
<td>GSD, FAO defect, Hyperinsulinism</td>
</tr>
<tr>
<td>Child</td>
<td>Accelerated starvation, Hypopituitarism</td>
</tr>
<tr>
<td>Adolescent</td>
<td>Insulinoma, Adrenal insufficiency</td>
</tr>
</tbody>
</table>

Relation to meal:

<table>
<thead>
<tr>
<th>Onset</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 hours</td>
<td>Galactosemia, Fructose intolerance</td>
</tr>
<tr>
<td>2-6 hours</td>
<td>Hyperinsulinism</td>
</tr>
<tr>
<td>6-12 hours</td>
<td>Glycogen storage disease</td>
</tr>
<tr>
<td>&gt; 12 hours</td>
<td>FAO defect, ketotic hypoglycemia</td>
</tr>
</tbody>
</table>

Hyperinsulinism:

- **History**
  - Onset (early KATP, late GCK, GDM)
  - Family history (familial forms)
  - Risk factors: IDM, β agonist Rx, HIE, UAC

- **Examination**
  - Ear crease anomaly, exomphalos, hemihyper trophy (BiW syndrome)
  - Macrosumia (KATP channel defect)

Medical management:

- **Diazoxide (5-20 mg/kg/day)**
  - First line agent (inertive in KATP defect)
  - Fluid retention (combine with triamide)
  - Hypertrichosis, low platelet, leukopenia

- **Octreotide (10 μg/kg/day)**
  - Effective in all forms, gastroparesis
  - Gut ischemia (risk of NEC)

- **Glucagon (5-20 μg/kg/hour SC)**
  - Insulin antagonist; effective in all forms
  - Indications: Cardiac failure

- **Nifedipine (0.1-0.3 mg/kg/day)**
  - Contraindications: In diazoxide
  - Recurrence following pancreatectomy
Persistent hyperinsulinism
Localisation studies

Focal lesion
Resection

Diffuse lesion
Diazoxide

No response
Sub-total pancreatectomy

Response
Diazoxide

Ketotic hypoglycemia

Lactate
High
Glucagon response

Normal
GH, cortisol

Organomegaly

Absent
GSD I

Present
GNG

Yes
GSD III, VI

No
Ketotic

Non-ketotic hypoglycemia

Urine reducing substance

Present
Galactosemia
HFI

Absent
Insulin

High
Hyperinsulinism

Normal
FAO defect