Neonatal Hypoglycemia

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Objective

Hypoglycemia-approach

Congenital Hyperinsulinism Infancy–management

Surgical Indications in Hypoglycemia & Post surgery - challenges

NHBI
Why are we worried about Hypoglycemia?
Neonatal Hypoglycemia
Brain injury

- Irreversible neuronal injury can result from hypoglycemia
- Hypoglycemic brain more vulnerable to damaging effects of ischemia
  - sick infants have increased requirement

MRI
Definition ???

- **Neonatal Hypoglycemia**: Operational threshold values of Blood Glucose less than 40mg/dl (plasma glucose level less than 45 mg/dl)

- All agree treatment for symptomatic infants
Symptoms

General
- Abnormal cry
- Poor feeding
- Hypothermia
- diaphoresis

Neurologic
- Tremors/jitteriness
- Irritability
- Lethargy
- Hypotonia
- seizures

Cardio respiratory
- Tachypnea
- Apnea
- cyanosis
Case Scenario

- Term male neonate born to non-consanguineously married 27 years old Primi gravida mother by caesarean section with a birth weight of 3500gms.
- Antenatal and peri-natal periods were uneventful.
- Screened because of poor feeding
- RBS-30 mg/dL

Whom to screen for hypoglycemia?
Whom to Screen ??

Anticipate

- Delayed initiation of breast feeding
- Low birth weight, IUGR, Pre-term
- Sepsis, polycythemia, Asphyxia
- Infant of diabetic mother, GDM, LGA babies
When to Screen ??

“SCHEDULE OF BLOOD GLUCOSE MONITORING”

<table>
<thead>
<tr>
<th>SYMPTOMATOLOGY OF INFANTS</th>
<th>TIME SCHEDULE FOR SCREENING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At risk neonates</strong> (LBW, Preterm, SGA, IDM, LGA, IUGR)</td>
<td>2, 6, 12, 24, 48, and 72 hrs</td>
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<tr>
<td><strong>Sick infants</strong> (Sepsis, asphyxia, shock in the active phase of illness)</td>
<td>Every 6–8 hrs (individualize as needed)</td>
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<tr>
<td><strong>Stable VLBW infants on parenteral nutrition</strong></td>
<td>Initial 72 hrs: every 6 to 8 hrs; after 72 hrs in stable babies: once a day</td>
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Infants exhibiting signs compatible with hypoglycemia at any time also need to be investigated

Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

![Graphical representation of glucose management strategies](image)

**Symptomatic and <40 mg/dL** → IV glucose

**Asymptomatic**

**Birth to 4 hours of age**

- **INITIAL FEED WITHIN** 1 hour
- **Screen glucose 30 minutes after 1st feed**
- **Initial screen <25 mg/dL**
  - **<25 mg/dL** → IV glucose
  - **25–40 mg/dL** → Refeed/IV glucose as needed

**4 to 24 hours of age**

- **Continue feeds q 2-3 hours**
- **Screen glucose prior to each feed**
- **Screen <35 mg/dL**
  - **<35 mg/dL** → IV glucose
  - **35 – 45 mg/dL** → Refeed/IV glucose as needed

**Target glucose screen ≥45 mg/dL prior to routine feeds**

* Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40–50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.
Case scenario

- In view of hypoglycemia did not improve with feeds was started on IV fluids with GIR 6 to 8 mg/kg/min
- Hypoglycemia persisted so GIR was increased by 2 mg/kg/min
- Gradually increased up to 20 mg/kg/min
- What next?
It may be difficult to identify and distinguish newborn infants with a persistent hypoglycemia disorder from those with transitional low glucose levels in the initial 48 hours of life.

The first few months of life are the most vulnerable period for developmental disability, which occurs in 25%-50% of children with congenital hyperinsulinism.

Early recognition and treatment are crucial for preventing these sequelae.
IV Therapy

- Infants with hyperinsulinemia may require >12 mg/kg/min IV glucose to maintain euglycemia
- Central IV access if using >12.5% dextrose
- Worry about fluid overload
- Weaning
  - Stable glucose 12-24 h
  - Follow preprandial glucose
  - Decrease infusion rate 10-20% each time glucose >50-60 mg/dl
Metabolic Clues to Hypoglycemia Diagnosis

Hypoglycemia

\[ \text{HCO}_3^-,\ \text{BOHB, Lactate, FFA} \]

No Acidemia

- BOHB↓, FFA↓
  - Genetic Hyperinsulinism
  - Hypopituitarism in newborns
  - Transitional Neonatal Hypoglycemia
  - Perinatal Stress Hyperinsulinism

- BOHB↓, FFA↑
  - Fatty Acid Oxidation Defects

Acidemia

- Lactate↑
  - Gluconeogenesis Defects

- BOHB↑
  - Ketotic Hypoglycemia
  - Glycogenoses
  - GH deficiency
  - Cortisol deficiency
<50 mg/dL

Increase GIR @ 2mg/kg/min till euglycemia

If GIR >12mg/kg/min for 24 hours or hypoglycaemia persist for >7 days (Persistent / Refractory Hypoglycemia)

Send -
Serum Insulin, cortisol & GH Level
Blood ammonia
Blood lactate
Free fatty acid levels
Urine ketones & reducing substance
Urine aminoacidogram

Drugs (Hydrocortisone, Diazoxide, Glucagon, Octreotide)
Case Scenario

- Evaluation showed high insulin levels 13.4 microIU/ml during hypoglycemia (sugar 24mg/dl)
- With no acidosis, normal lactate, normal ketoacids and urine showed no ketone body
- Newborn metabolic screening was also normal.
- Patient was diagnosed as a case of hyperinsulinemic hypoglycemia
Case Scenario

- He was not responsive to
  - 20mg/kg/min IV dextrose infusion
  - optimum dose of diazoxide (20mg/kg/day)
  - octreotide (30ug/kg/day)
  - Hydrocortisone

- what next?
  - Role of genetic studies
  - Indication for surgery
  - PET Scan??
Congenital Hyperinsulinism Infancy

- CHI is a heterogeneous disorder associated with nine known mutations.
- β cell- potassium ATP (K ATP) channel genes ABCC 8 (SUR 1, MIM # 256450) and KCNJ 11 (Kir 6.2, MIM # 601820) being commonest among all.
Pedigree of Patient with CHI harbouring ABCC8 mutation

N/N
Asymptomatic

M/N, 27yrs, carrier
Asymptomatic
Gene-ABCC8
DNA-C.4253G>A, Protein-(Arg1418His)

M/N, 3.5kg, CHI.
Gene-ABCC8
DNA-C.4253G>A, Protein-(Arg1418His)
Missense mutation
KCNJ11, paternal ABCC8 at risk of focal

Seminars in Pediatric Surgery (2011) 20, 32-37
Patient under went a near total pancreatectomy at the age of 18 days.
<table>
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<tr>
<th>Day</th>
<th>Action</th>
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| Day 1 | Establish diagnosis of HI  
Begin 5-d trial of diazoxide  
If HI is severe begin at max dose (15 mg/kg/d)  
If HI less severe/perinatal-stress, start diazoxide at 5-10 mg/kg/d*  
Consider starting a diuretic with diazoxide, especially if on high GIR |
| Day 2-5 | Determine minimum GIR required to maintain blood glucose between 70 and 100  
If HI is severe or GIR is >10 mg/kg/min, send mutation analysis on HI genes for infant and parents |
| Day 6  | Determine fasting tolerance on diazoxide  
Failure to fast >12 h with BS >70 mg/dL indicates diazoxide unresponsiveness  
Diazoxide failure suggests a $K_{ATP}$ channel HI and potential surgical candidate  
Begin arrangements for transfer to a specialized HI center with $^{18}$F-DOPA PET scan capability |
| Day 7  | Discontinue diazoxide; consider octreotide, 5 $\mu$g kg$^{-1}$ d$^{-1}$ divided every 6-8 h  
Desensitization to octreotide is common after 2-3 doses  
If required, octreotide can be increased to maximum of 15 $\mu$g/kg/d |
| Day 8-14 | Evaluate effectiveness of octreotide with fasting test while awaiting transfer of patient |
Post-operative infant remain hypoglycemic, even after diazoxide, octreotide and nifedipine (0.75 mg/kg/day in divided doses) and glucose infusion rate remain high (14 mg/kg/min) to maintain euglycemia.
Sirolimus

- Enteral sirolimus was considered at dose of 0.5 mg/kg/day and subsequently it was increased to 1 mg/kg/day.
- Gradually IV dextrose infusion was tapered and baby achieved normal blood sugar levels with oral feed (180 ml/kg/day) and medications.

Senthil seniappan NEJM 2014
Sirolimus

- A possible mechanism of betacell hyperplasia in CHI involves constitutive activation of mTOR pathway.
- The mechanisms of action of sirolimus in hyperinsulinemic hypoglycemia has not fully understood but probably the effect on betacell mass is achieved through inhibition of mTOR complex1 (mTORC1) pathway, induce chronic insulin resistance by inactivation of mTORC2 pathway and decreased function and viability of betacell by down regulation of prosurvival protein kinase B5.
After 2 weeks of sirolimus treatment baby was discharged home with sirolimus diazoxide, and octreotide.

Over next 4 weeks diazoxide dose was reduced and octreotide was tapered and stopped with blood sugar monitoring.

At 8 months follow up infant is maintaining euglycemia with oral sirolimus (0.5mg/kg/day) and diazoxide (10mg/kg/day), we did not notice any major side effects to sirolimus and development of child was appropriate for age.
At 3, 6, 9, 12 and 18 months corrected age they can be followed up for growth, neurodevelopment, vision and hearing loss.

MRI at 4-6 weeks provides a good estimate of hypoglycemic injury and therefore should be considered in follow up of such infants subject to affordability.
Asymptomatic Hypoglycemia: Is it as bad as symptomatic hypoglycaemia?
Neonatal Hypoglycemia

- CHYLD study (Children with Hypoglycemia and Their Later Development) study
  - 528 babies prospective at risk of hypoglycemia
  - Plasma glucose >47mg/dl for 48 hours after birth
  - 404 babies - Development outcome at 2 years
  - 53% had hypoglycemia
  - With treatment 25% had 5 hours of low glucose
  - The lowest blood glucose concentration, number of hypoglycemia episodes did not predict
  - No adverse outcome

Mckinley et al, NEJM oct 2015
Unexpectedly higher glucose level after treatment – neurosensory impairment

**ISSUES RAISED**

- Management?
- Undetected hypoglycemia
- Congenital Hyperinsulinism- continue permanent brain damage
Association Between Transient Newborn Hypoglycemia and Fourth-Grade Achievement Test Proficiency: A Population-Based Study

Kaiser J R et al. JAMA Pediatr 24th August 2015

- Retrospective cohort
- 1395 neonate-student pairs (10 yrs age)
- Transient, asymptomatic hypoglycaemia <35, <40, <45 mg/dL
- School proficiency in Mathematics and literacy

- Neonates with hypoglycaemia had significantly lower probability of proficiency in Literacy and mathematics in 4th grade scores

- Need to be confirmed in other populations and prospective cohorts
In summary

- No uniform consensus on definition but all agree to treat symptomatic infants
- Protocol based screening and evaluation of neonates with persistent hypoglycemia
- Development follow up
- Method of screening and treatment of transient hypoglycemia need more studies