Current Medical Treatment Options for Hyperinsulinism

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Goals of therapy in hyperinsulinism

- **Immediate:**
  - To promptly restore plasma glucose to the normal range [>70 mg/dL(3.9 mmol/L)]
- **Mid-term:**
  - To identify optimal treatment regimens according to type of hyperinsulinism
  - To maintain normal plasma glucose concentrations within the normal range while encouraging normal feeding/diet
- **Long-term:**
  - To prevent brain damage
  - To promote normal life and development

De Leon, Arnoux, Banerjee, et al. *Horm Res Paediatr*, 2023

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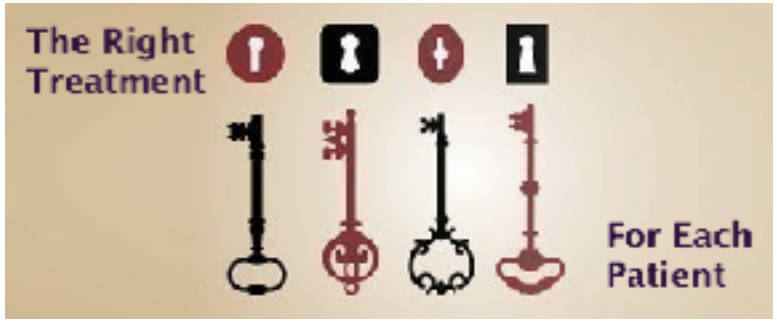
Aspirational goals for treatment of HI

➢Individualized treatment plan:

- According to genotype (genetic testing results)
- According to the phenotype (clinical manifestations)
  - Protein-induced hypoglycemia: K_{ATP}-HI, GDH-HI, SCHAD-HI
  - Impaired glucagon secretion: K_{ATP}-HI, GCK-HI

➢Requires:

- Comprehensive investigations to understand all aspects of the condition
- Different treatment options – one treatment modality may "not fit all"



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Diazoxide

- First-line of therapy for hyperinsulinism
- Dose:
  - 5-15 mg/kg/day by mouth dosed twice daily
  - Suspension (50 mg/mL) or capsules
- Side effects:
  - Edema (18%) – concomitant use of diuretics recommended
  - Pulmonary hypertension (2.1%-4.8%)
  - Neutropenia (15.6%)
  - Thrombocytopenia (4.7%)
  - Hyperuricemia (5%)
  - Hypertrichosis (84%), coarsening of facial features (24%)
- Screening for side effects:
  - Echocardiogram:
    - ~ 1 week after initiation
  - Laboratory studies:
    - Blood counts, chemistry, uric acid every 6 months

De Leon, Arnoux, Banerjee, et al. *Horm Res Paediatr*, 2023
Herrerra, et al. *J Clin Endocrinol Metab*, 2018
Thornton, et al. Horm Res Paediatr, 2019
Welters A, et al. *Orphanet J Rare Dis*, 2015; 10:150

Diazoxide

- Responsiveness to diazoxide:
  - Demonstrated by showing that hypoketotic hypoglycemia has been reversed
  - In practice, demonstrating that the infant or child can fast and generate hyperketonemia prior to developing hypoglycemia

- Phenotypic characterization:
  - Identification of infants that need additional evaluation for the possibility of focal disease

De Leon, Arnoux, Banerjee, et al. *Horm Res Paediatr*, 2023

Octreotide

- Somatostatin analogues - second line treatment for:
  - Diazoxide-unresponsive cases
  - Unacceptable diazoxide side effects
  - Diazoxide not available
- Dosing: 5-20 mcg/kg/day by subcutaneous injection
  - ✓ Every 6 hrs
  - ✓ Given 2 times a day in combination with continuous intragastric dextrose or continuous enteral feedings
  - ✓ Continuous subcutaneous administration through a pump
- Effectiveness:
  - ✓ Tachyphylaxis common
- Long-acting formulations
  - ✓ Dosed once a month
  - ✓ Octreotide LAR
  - ✓ Lanreotide

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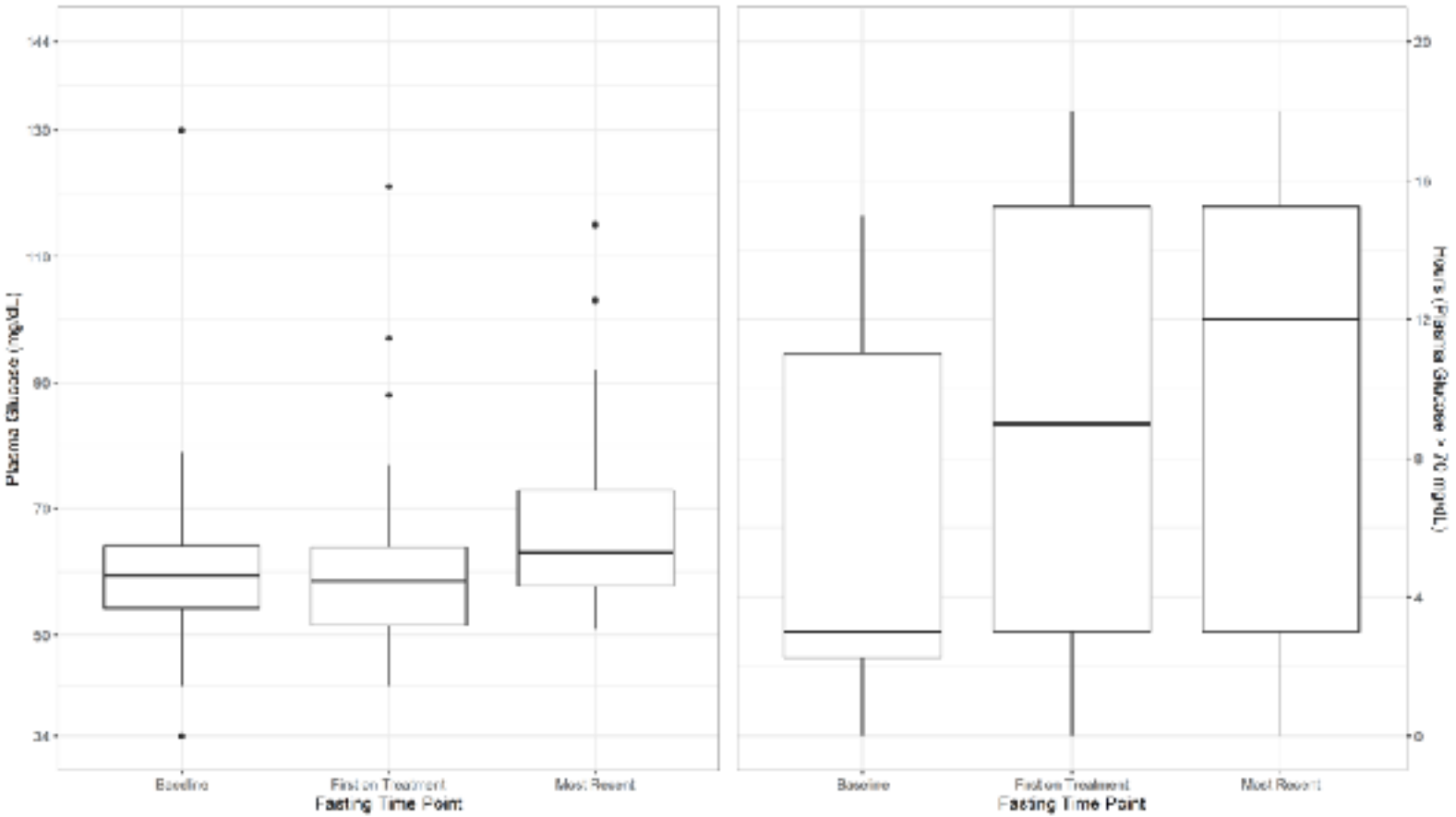
De Leon, Arnoux, Banerjee, et al. *Horm Res Paediatr*, 2023

Use of *lanreotide* in the treatment of HI

- Lanreotide
  - Somatostatin analogue
  - Deep subcutaneous injection every 28 days
  - Dose: 30-90 mg
- Our experience:
  - 54 children and adults with HI
  - Median age: 4.6 years (1.5-28.5)
  - Genetics: 63% K_{ATP}HI
  - Response: 42% able to discontinue other treatments and managed on lanreotide alone
  - Side effects: subcutaneous nodules (26%), gallstones (11%)



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Cuff, Lord, Stewart, De Leon. *J Clin Endocrinol Metab*, 2022

Somatostatin Analogues

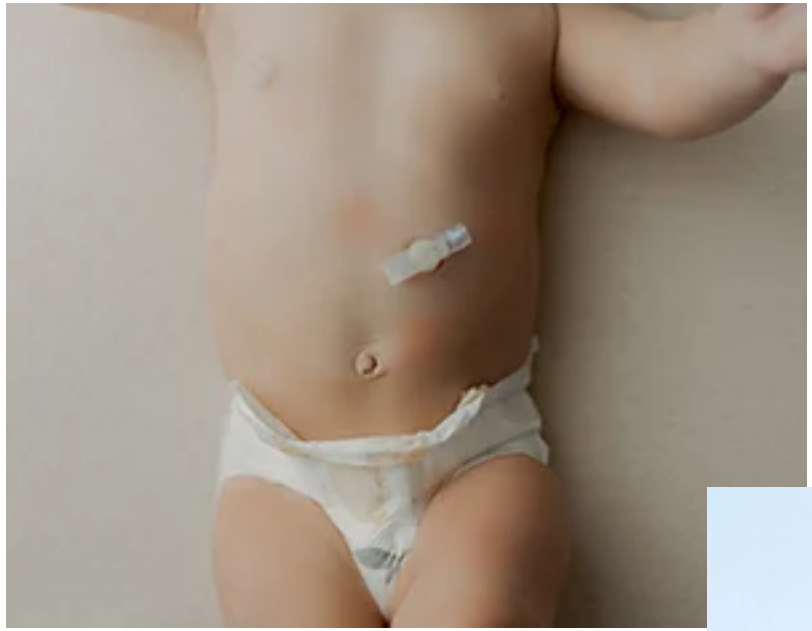
- Side effects:
  - ✓ Suppression of growth and thyroid function
  - ✓ GI side effects
  - ✓ Gall bladder pathology (32%)
  - ✓ Transient elevation of LFTs (46.4%)
  - ✓ Thrombosis (2%)
  - ✓ Necrotizing enterocolitis (1%)
- Screening for side effects:
  - Growth and weight gain
    - Every 6 months
  - Gallbladder ultrasound:
    - Every 6 months
  - Laboratory studies:
    - Every 6 months
    - Liver function tests, growth factors, thyroid function tests, fat-soluble vitamin levels

Herrerra, et al. *J Clin Endocrinol Metab*, 2018
Welters A, et al. *Orphanet J Rare Dis*, 2015; 10:150
Demirbilek, et al. J Clin Endocrinol Metab, 2014
McMahon, et al. *Pharmacoepidemiol Drug Saf,* 2017
De Leon, Arnoux, Banerjee, et al. *Horm Res Paediatr,* 2023

Continuous Intragastric Dextrose

- Dosing:
  - ✓D10-20%
  - ✓Not more than 10 mg/kg/min
  - ✓Continuously by gastrostomy
  - ✓Requires an infusion pump

- Side effects:
  - ✓Vomiting 33%
  - ✓Diarrhea 4.8%
  - ✓Tube/pump malfunction 57%



Vajravelu, et al. *Horm Res Paediatr*, 2018

How do we determine treatment responsiveness?

- Fasting test:
  - Duration depending on the age of the child:
    - 12-18 hrs
  - Monitor:
    - Glucose and ketone levels
  - Effectiveness:
    - Goal is to maintain euglycemia while receiving an age-appropriate feeding regimen, allowing for periods of fasting at night

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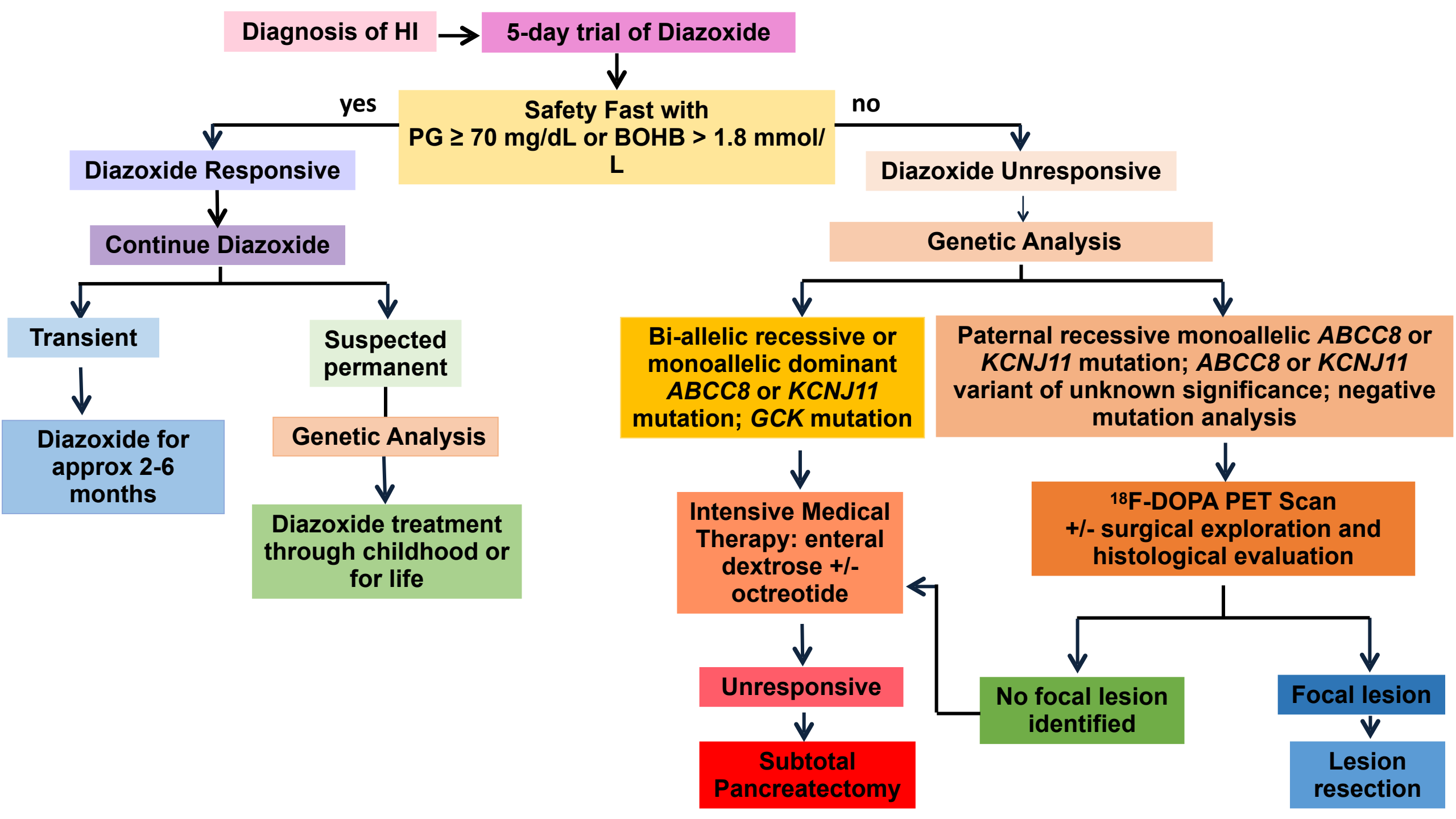
Diagnosis of HI
5-day trial of Diazoxide
Safety Fast with PG ≥ 70 mg/dL or BOHB > 1.8 mmol/L
yes
no
Diazoxide Responsive
Continue Diazoxide
Transient
Diazoxide for approx 2-6 months
Suspected permanent
Genetic Analysis
Diazoxide treatment through childhood or for life
Diazoxide Unresponsive
Genetic Analysis
Bi-allelic recessive or monoallelic dominant ABCC8 or KCNJ11 mutation; GCK mutation
Paternal recessive monoallelic ABCC8 or KCNJ11 mutation; ABCC8 or KCNJ11 variant of unknown significance; negative mutation analysis
Intensive Medical Therapy: enteral dextrose +/- octreotide
Unresponsive
Subtotal Pancreatectomy
18F-DOPA PET Scan +/- surgical exploration and histological evaluation
No focal lesion identified
Focal lesion
Lesion resection

Follow-up

- Ongoing monitoring
  - For side effects of therapy
  - Glycemic control:
    - ✓ Glucose meter vs. CGMS
    - ✓ Inpatient evaluations: safety fast
  - Growth and development
- Discontinuation of treatment
  - Depends on type of hyperinsulinism
  - Normal plasma glucoses on minimal treatment support
  - When resolution is suspected
    - ✓ Transient hyperinsulinism
    - ✓ Focal cases
  - Importance of demonstrating resolution
    - ✓ Fasting test

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Thank You

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