HYPERINSULINISM IN INFANTS

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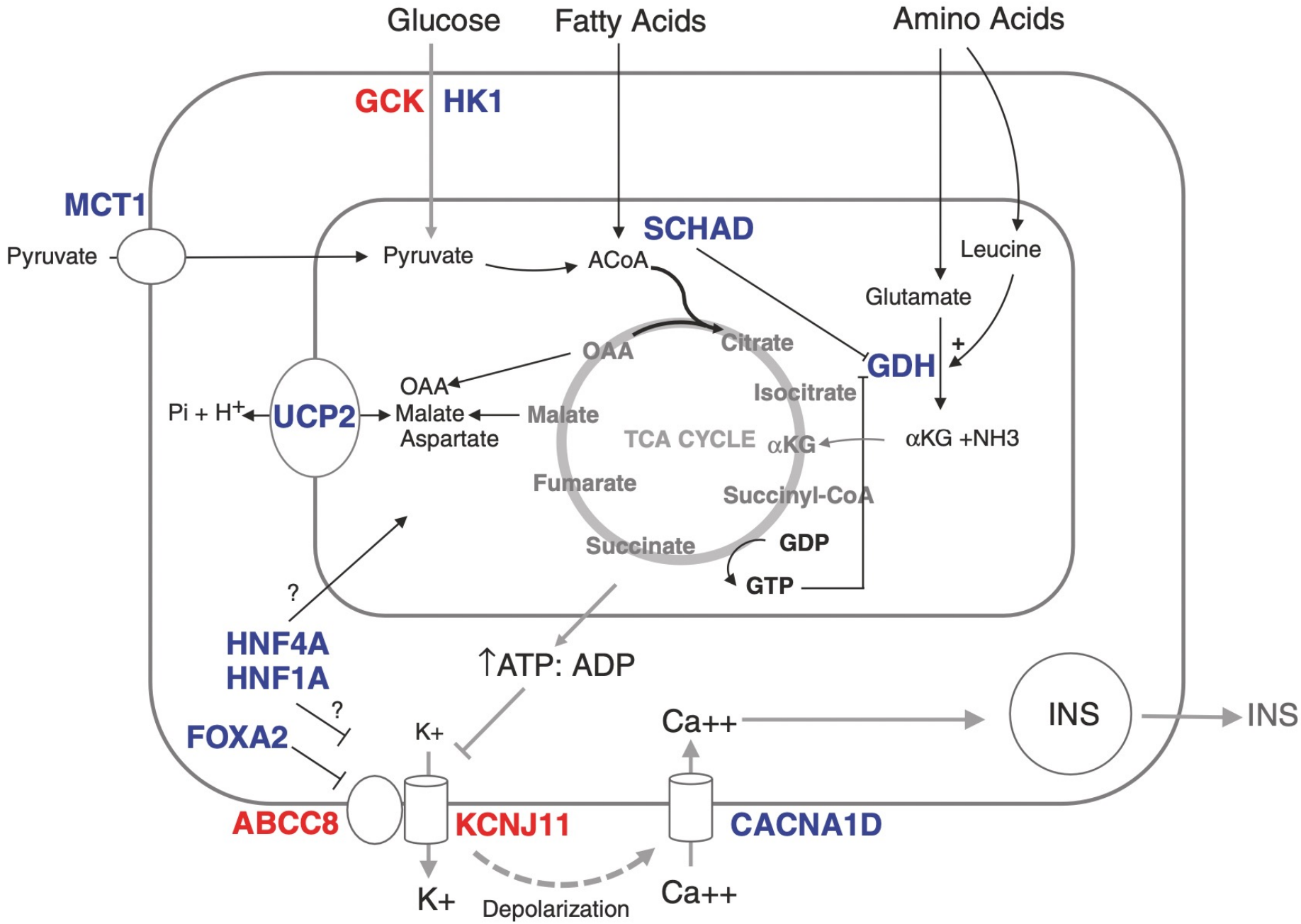
CHILDREN'S MEDICAL CENTER

- B/W 3950
- BS 20-30 in the first 48 h of life
- Episodes of convulsion in the first 3 months of life
- At 3 months BS: 38
- GIR >10mg/Kg/Min
- Urine ketone : neg
- At BS:38 insulin level: 13micU/mL

Risk factors for perinatal stress induced HI

Maternal diabetes
SGA/IUGR
Preeclampsia/maternal hypertension
Birth asphyxia
Prematurity
Erythroblastosis fetalis


Glucose
Fatty Acids
Amino Acids
GCK
HK1
MCT1
Pyruvate
Pyruvate
SCHAD
ACoA
Leucine
Glutamate
+
GDH
OAA
Citrate
OAA
Isocitrate
Pi + H+
UCP2
Malate
Aspartate
Malate
TCA CYCLE
αKG
αKG +NH3
Fumarate
Succinyl-CoA
Succinate
GDP
GTP
?
HNF4A
HNF1A
↑ATP: ADP
?
FOXA2
K+
Ca++
INS
INS
ABCC8
KCNJ11
CACNA1D
K+
Depolarization
Ca++

Causes of Hyperinsulinism

- Diazoxside responsive HI
- Diazoxide unresponsive HI
- Syndromic HI (Beckwith- Wiedemann, Kabuki, Sotos, Turner)

Criteria for Defining Diazoxide-Responsiveness

While on diazoxide treatment (≤15 mg/kg/day):

- Correction of fasting hypoketotic hypoglycemia:
  - Plasma BOHB >2.0 mmol/L *before* plasma glucose drops below 2.8–3.3 mmol/L (50–60 mg/dL)
    OR
  - Able to fast ≥18 h with plasma glucose >3.9 mmol/L (>70 mg/dL) with some increase in BOHB
- Correction of food-induced hypoglycemia if present (e.g., protein-sensitive hypoglycemia in GDH-HI, K_{ATP}-HI, SCHAD-HI; carbohydrate-induced hypoglycemia in UCP2-HI)

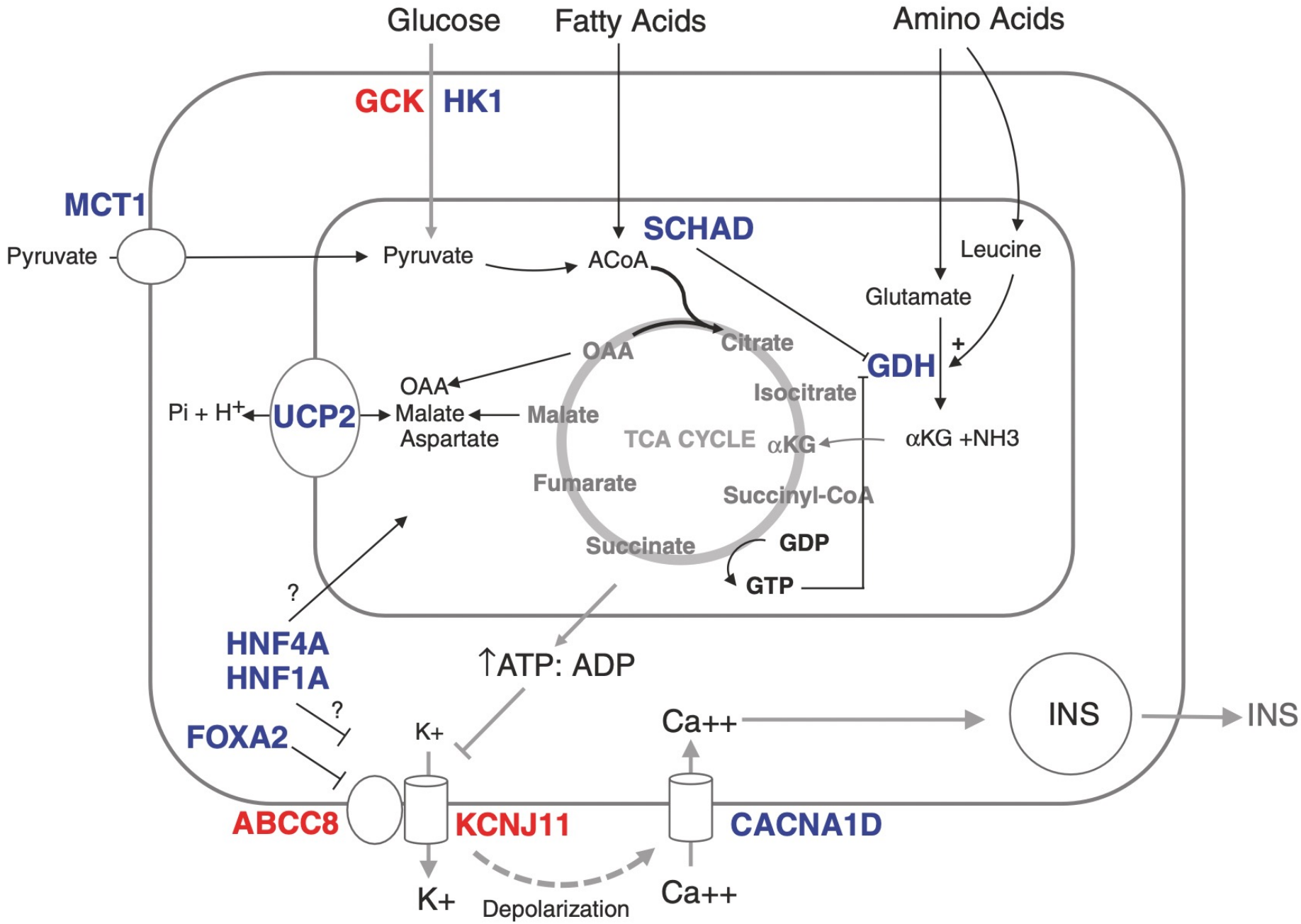

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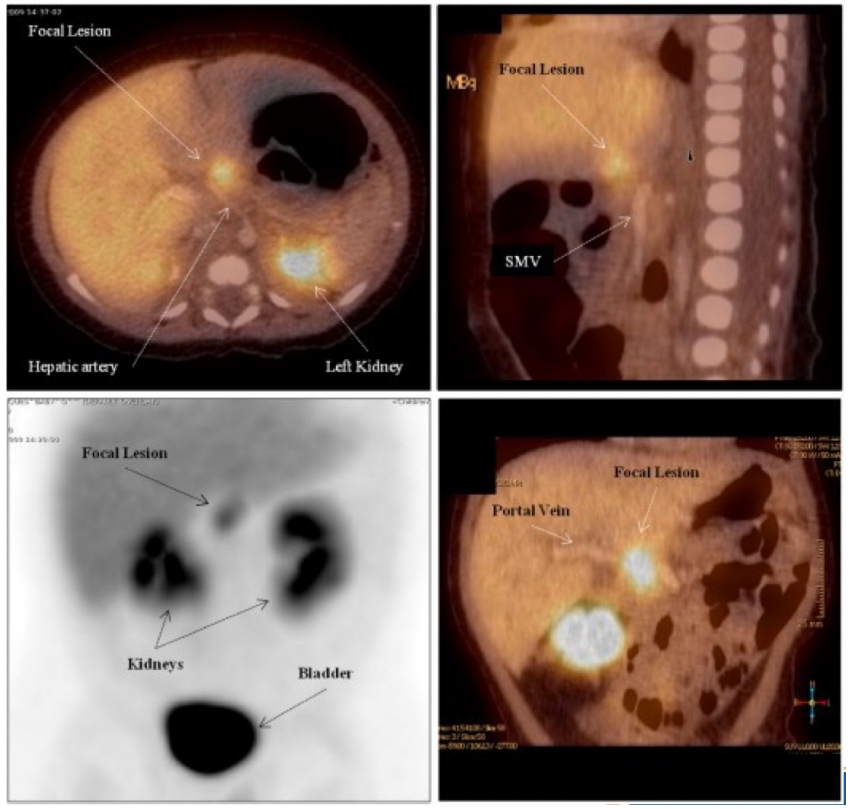
Table 3.1 K_{ATP} channel mutations leading to hyperinsulinism

K_{ATP} channel mutations	Diazoxide responsiveness	Mode of inheritance	Histology	Birth weight	Time of hypoglycemia presentation	Treatment
Recessive	Unresponsive	Paternally inherited recessive mutation with somatic loss of heterozygosity for the maternal 11p region → paternal isodisomy	Focal disease	Lower likelihood of LGA compared to diffuse disease	Days to weeks after birth	Curative limited pancreatectomy
		Biallelic recessive mutations	Diffuse disease	LGA	Birth to within few days of birth	Medical therapy, if unresponsive may need subtotal pancreatectomy
Dominant	Unresponsive	Autosomal dominant mutations	Diffuse disease	LGA	Birth to within few days of birth	Medical therapy, if unresponsive may need subtotal pancreatectomy
	Responsive	Autosomal dominant mutations	Diffuse disease	LGA	Asymptomatic to mild disease that presents days to weeks after birth	Diazoxide

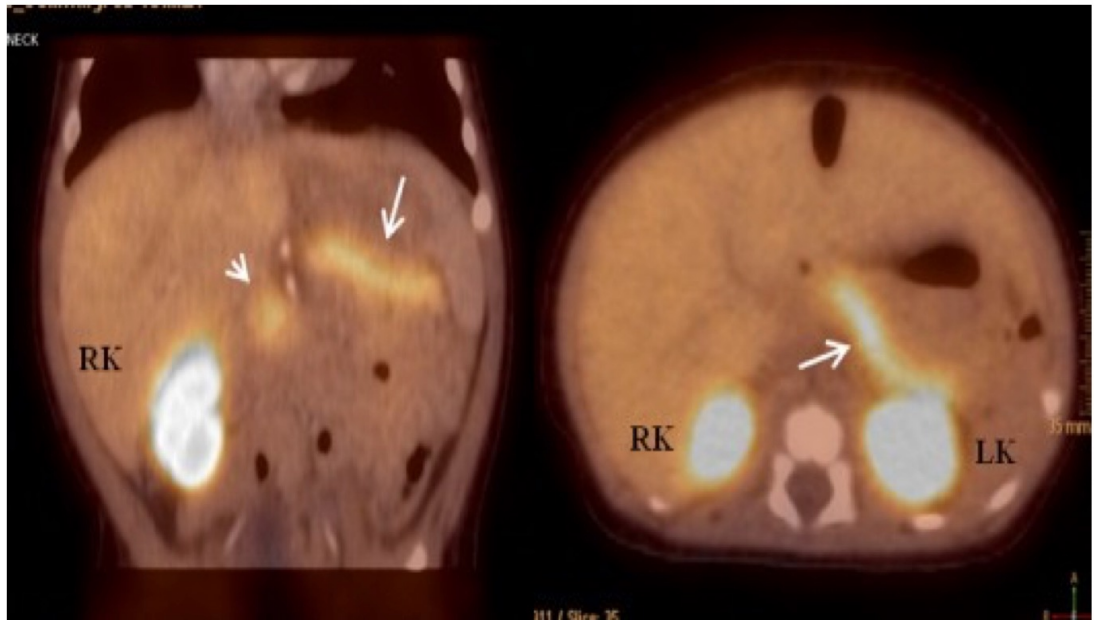
LGA large for gestational age

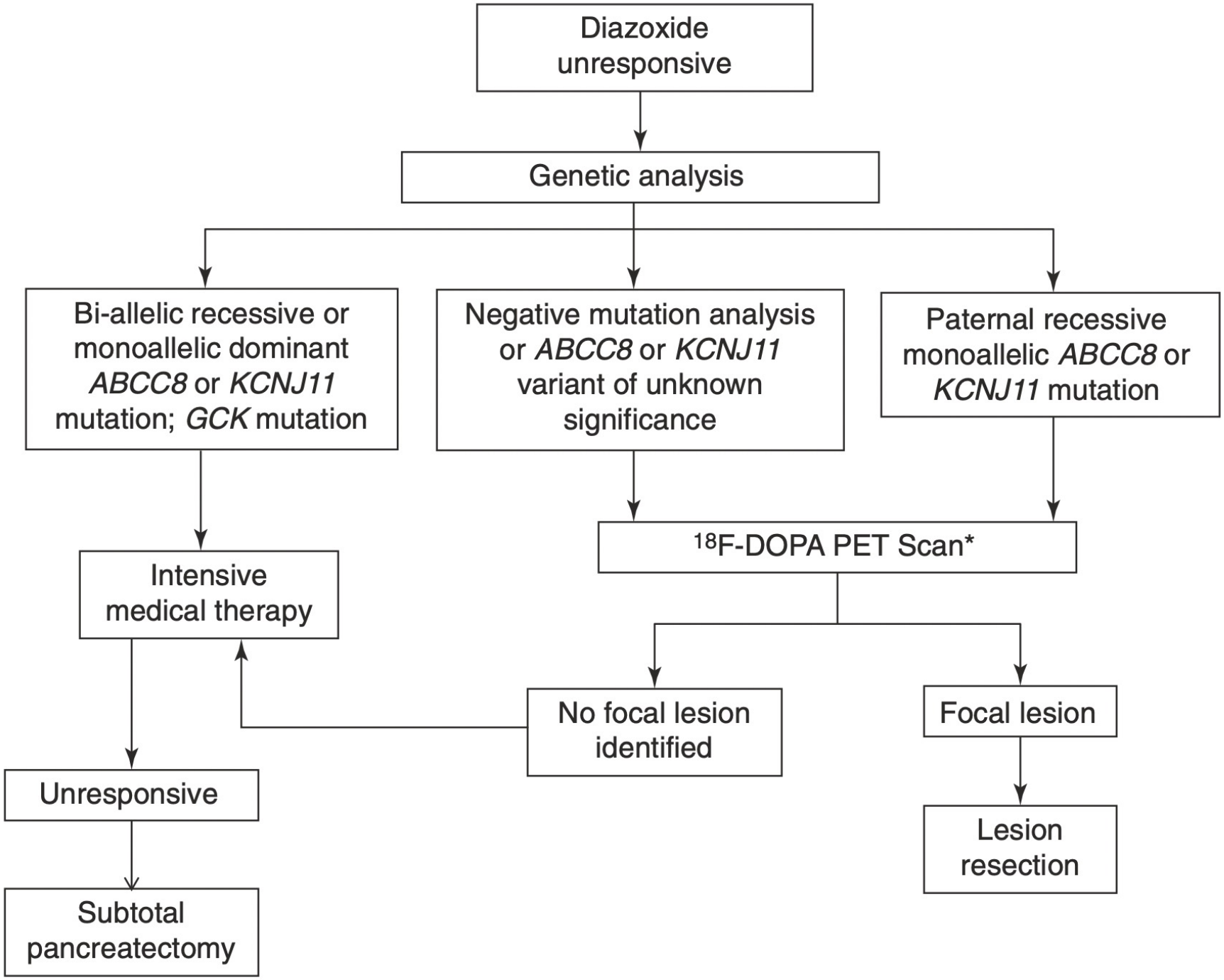
18F-DOPA PET SCAN

Focal Pet/CT scan



Diffuse PET/CT scan




Diazoxide unresponsive
Genetic analysis
Bi-allelic recessive or monoallelic dominant *ABCC8* or *KCNJ11* mutation; *GCK* mutation
Negative mutation analysis or *ABCC8* or *KCNJ11* variant of unknown significance
Paternal recessive monoallelic *ABCC8* or *KCNJ11* mutation
Intensive medical therapy
^{18}F-DOPA PET Scan*
No focal lesion identified
Focal lesion
Unresponsive
Lesion resection
Subtotal pancreatectomy

- Ammonium: 34
- 3- hydroxybutyrylcarnitine: NL
- Urine 3-hydroxyglutarate: NL
- 68 GA DOTATATE scan: NO focal lesion
- Severe vomiting with DZ
- Octreotide responsive
- Scheduled for operation

Table 2: Drugs used in medical management of hyperinsulinemic hypoglycemia

Medication	Route of administration	Dose	Side effects
Diazoxide	Oral	3-15 mg/kg/day	Fluid retention Hypertrichosis
Thiazide diuretics			
Chlorothiazide	Oral	5-10 mg/kg/day	Electrolyte
Hydrochlorothiazide	Oral	1-2 mg/kg/day	Imbalance
Octreotide	SC bolus, IV or SC infusion	5-35 µg/kg/day	Feed intolerance Steatorrhea Cholelithiasis Growth suppression
Long-acting octreotide (LAR/Lanreotide)	Deep SC IM	30-60 mg/dose Every 4 weeks	Same as octreotide
Sirolimus	Oral	0.5-1 mg/m^2/day	Heaptic and renal impairment Immunosupression
Glucagon	SC or IM	0.5-1 mg/dose	Skin rash Thrombocytopenia Feed intolerance
	Bolus IV or SC infusion	1-20 µg/kg/h	
Nifedipine	Oral	0.25-2.5 mg/kg/day	Dizziness Hypotension

SC – Subcutaneous; IM – Intramuscular; IV – Intravenous; Ca^{++} – Calcium; LGA – Large for gestational age

Long Acting Somatostatin Analogues

Sandostatin® LAR Depot (octreotide acetate) for injectable suspension dosing options

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A Multicenter Experience with Long-Acting Somatostatin Analogues in Patients with Congenital Hyperinsulinism

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Based on our common experience, we recommend the following:

- Consider long-acting somatostatin analogues in diazoxide-unresponsive patients after a trial of treatment with octreotide. If octreotide is effective and no severe side effects occur after a trial period, lanreotide (start dosage 30–60 mg subcutaneously every 4 weeks) or sandostatin-LAR (start dosage 10 mg intramuscularly every 4 weeks) could be considered.
- Avoid treatment with somatostatin analogues in patients with an increased risk of necrotizing enterocolitis.
- Patients receiving long-acting somatostatin analogue treatment should be monitored by blood glucose monitoring and/or continuous subcutaneous glucose monitoring to ensure satisfactory treatment response.
- Monitor liver enzymes every 4–6 weeks and repeat abdominal ultrasound every 3–6 months. If (asymptomatic) cholelithiasis is present, ursodeoxycholic acid may be added to the treatment regimen.
- Monitor growth and thyroid function at least 6-monthly. If tests indicate hypothyroxinemia, levothyroxine treatment may be required.