Neonatal Hypoglycemia

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Objective

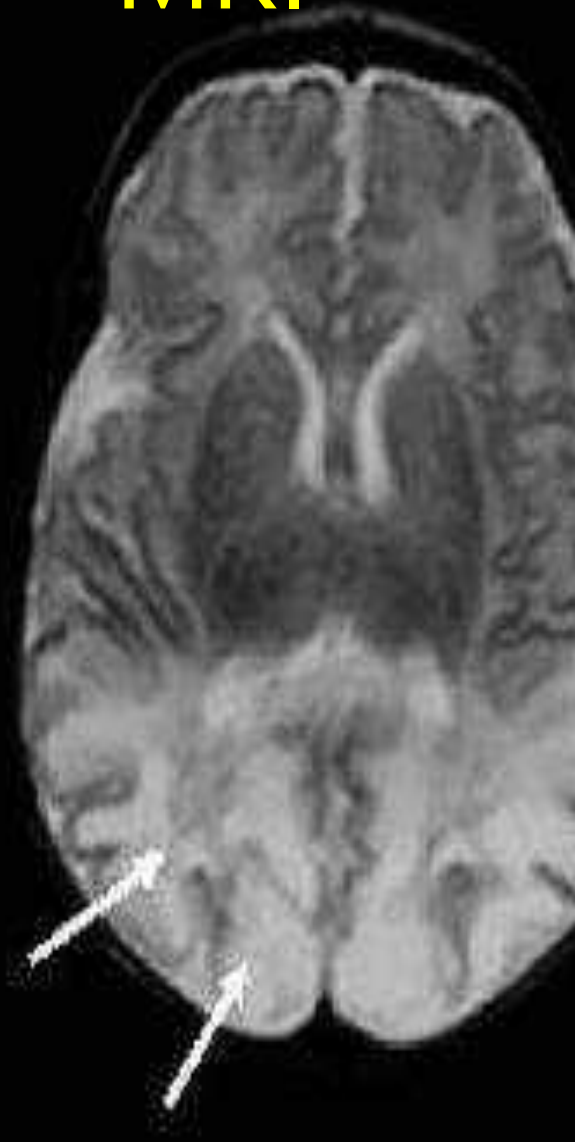
- Hypoglycemia-approach
- Congenital Hyperinsulinism Infancy–management
- Surgical Indications in Hypoglycemia & Post surgery - challenges
- NHBI

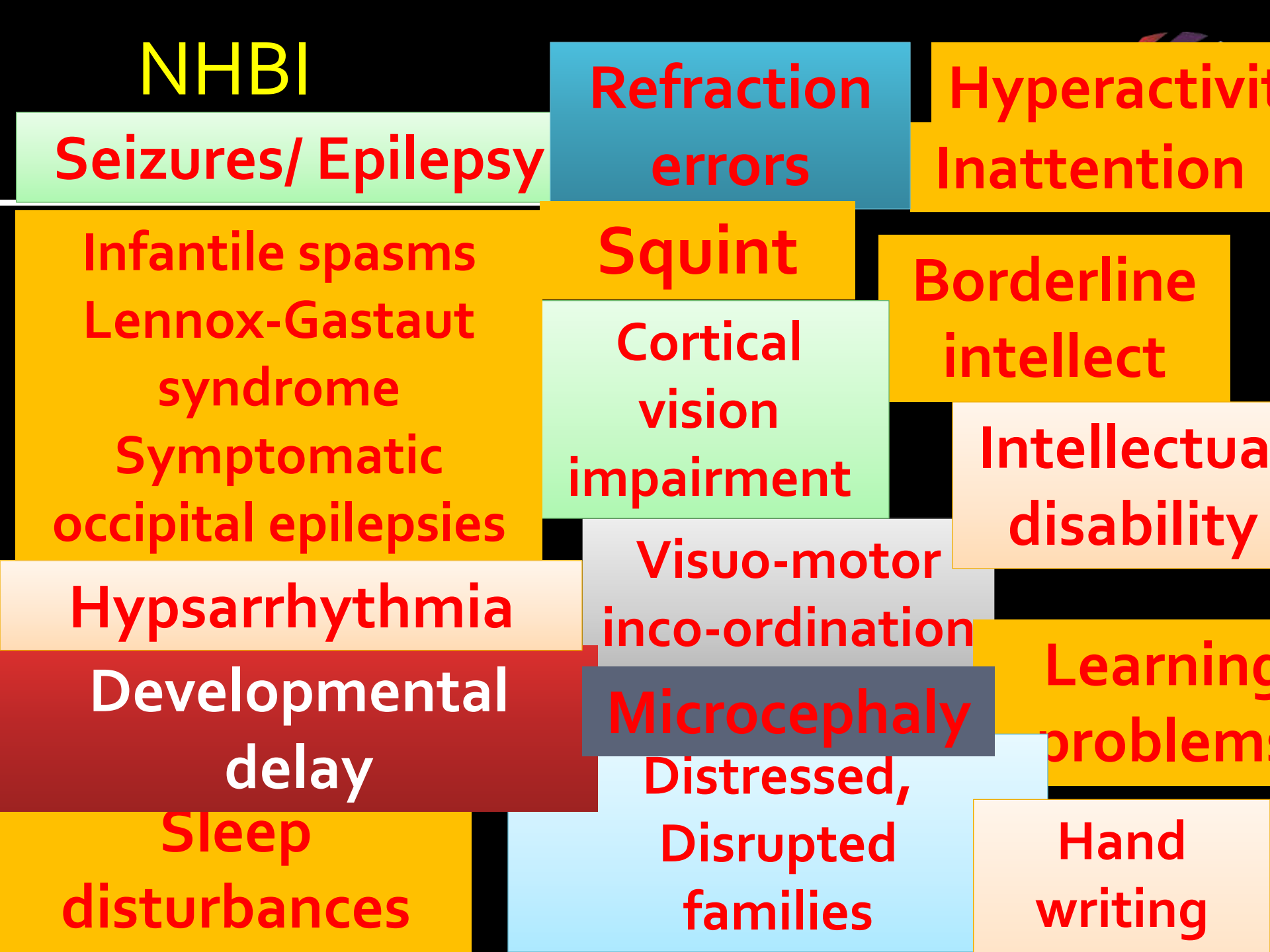
Why are we worried about Hypoglycemia?

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




NHBI
Seizures/ Epilepsy
Refraction errors
Hyperactivit
Inattention
Infantile spasms
Lennox-Gastaut syndrome
Symptomatic occipital epilepsies
Squint
Cortical vision impairment
Borderline intellect
Intellectua
disability
Hypsarrhythmia
Visuo-motor inco-ordination
Developmental delay
Microcephaly
Learning
problems
Sleep disturbances
Distressed, Disrupted families
Hand writing

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"

SYMPTOMATOLOGY OF INFANTS	TIME SCHEDULE FOR SCREENING
• **At risk neonates** (LBW, Preterm, SGA, IDM, LGA, IUGR)	2, 6, 12, 24, 48, and 72 hrs
• **Sick infants** (Sepsis, asphyxia, shock in the active phase of illness)	Every 6–8 hrs (individualize as needed)
• **Stable VLBW infants on parenteral nutrition**	Initial 72 hrs: every 6 to 8 hrs; after 72 hrs in stable babies: once a day

Infants exhibiting signs compatible with hypoglycemia at any time also need to be investigated

Jain A, Aggarwal R, Jeeva Sankar M, Agarwal R, Deorari AK, Paul VK. Hypoglycemia in the newborn. Indian J Pediatr. 2010 Oct;77(10):1137-42.

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

[(LPT) Infants 34 – $36^{6/7}$ weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)]

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

Feed and check in 1 hour

- <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

Feed and check in 1 hour

- <35 mg/dL ↓ IV glucose*
- 35 – 45 mg/dL ↓ Refeed/IV glucose* as needed

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

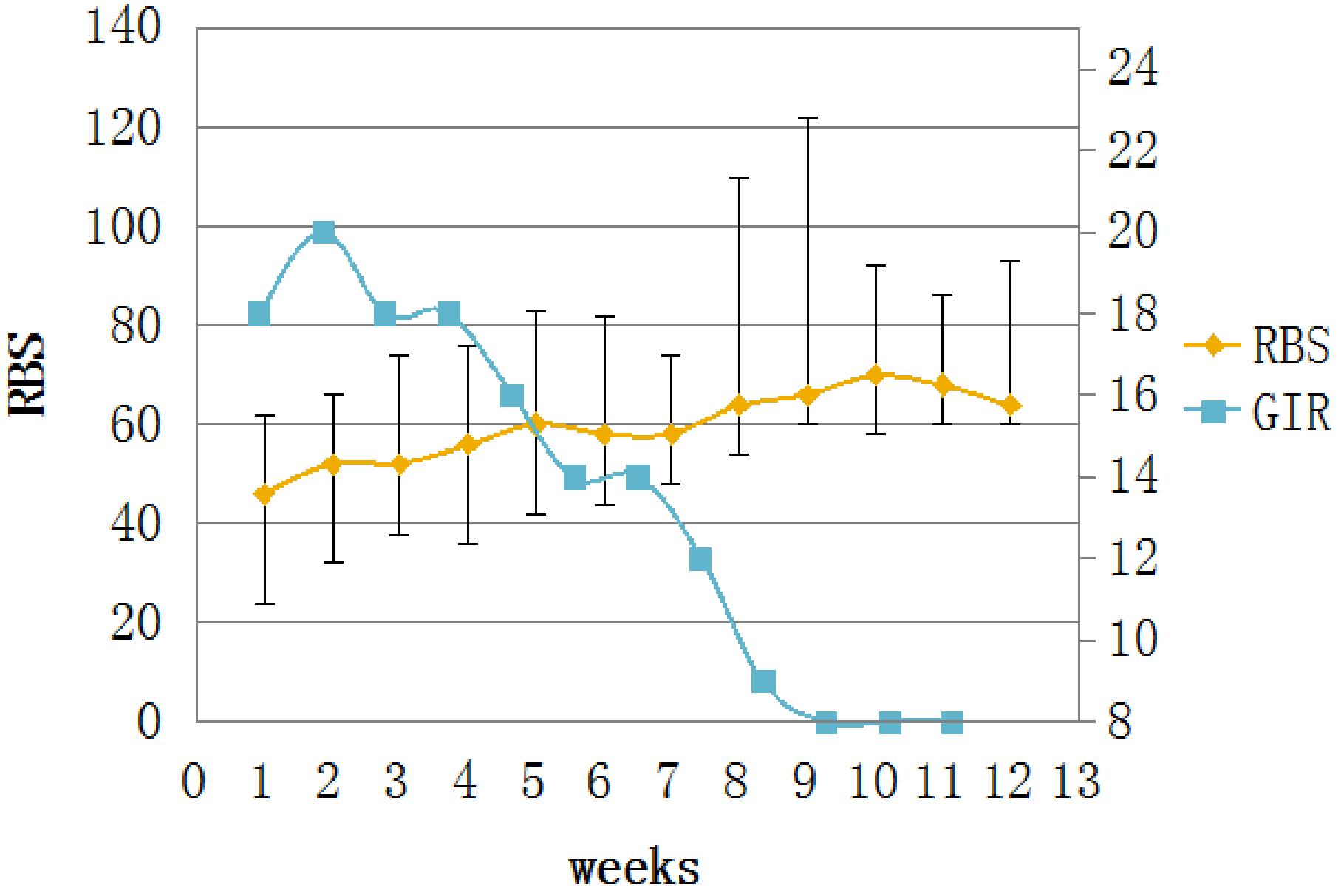
* Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

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

PEDIATRICS®

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 upto 20 mg/kg/min
- What next?


RBS
140
120
100
80
60
40
20
0
24
22
20
18
16
14
12
10
8
0 1 2 3 4 5 6 7 8 9 10 11 12 13
weeks
RBS
GIR

Congenital Hyperinsulinsim

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,

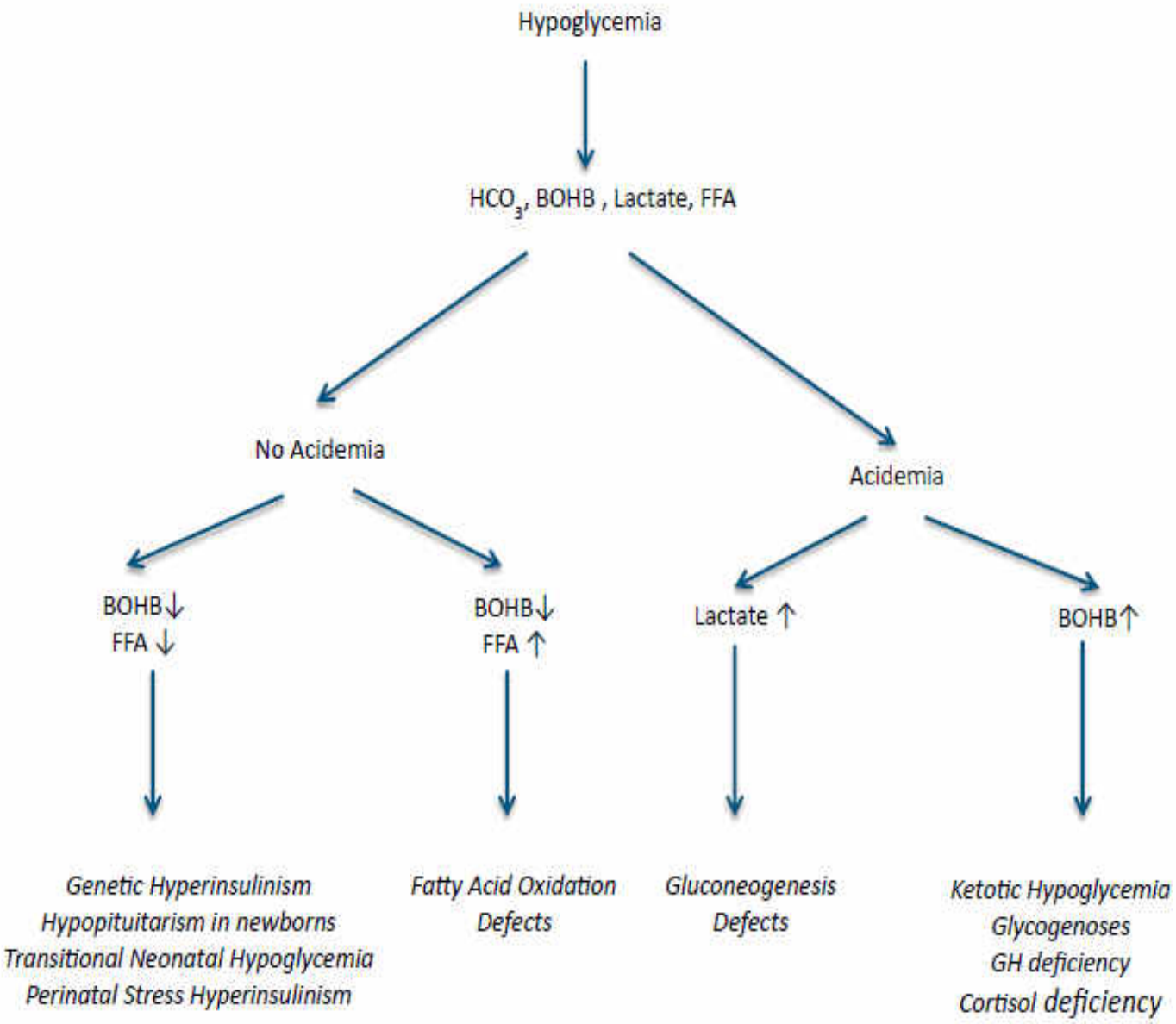
The first few months of life are the most vulnerable period for developmental disability, which occurs in 25%-50% of children with congenital hyperinsulinism.

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



<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)

↓

<u>Send</u> -

Serum Insulin, cortisol & GH Level

Blood ammonia

Blood lactate

Free fatty acid levels

Urine ketones & reducing substance

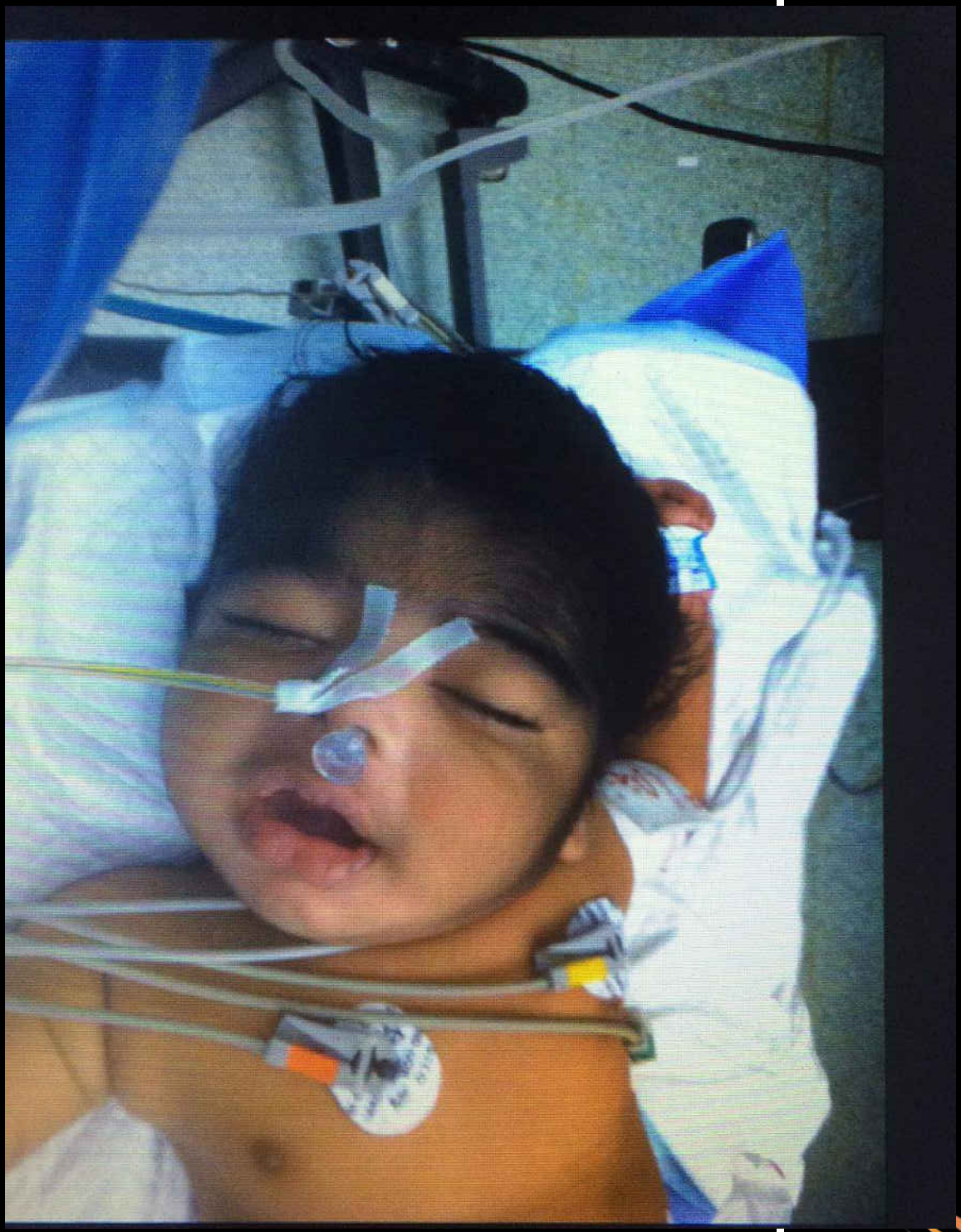
Urine aminoacidogram

↓

Drugs (Hydocortisone, 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

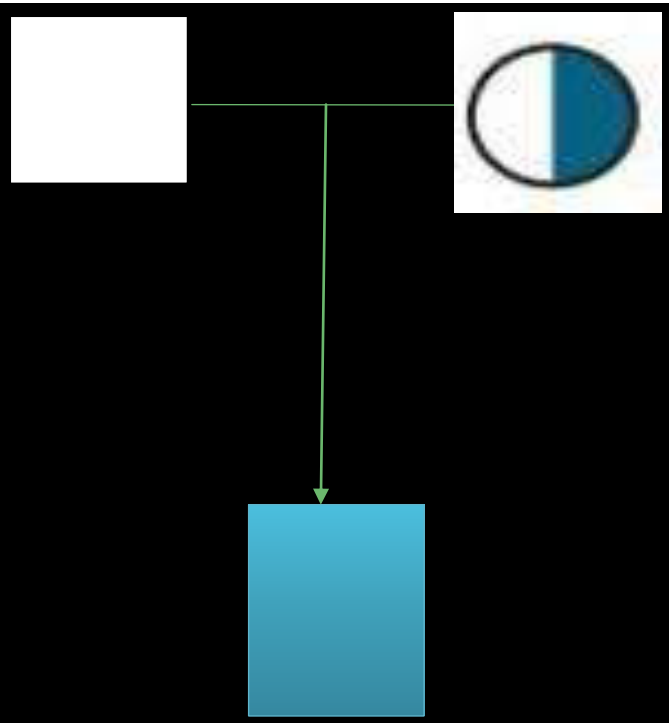
- He was not responsive to
  - 20mg/kg/min IV dextrose infusion
  - optimum dose of diazoxide (20mg/kg/day)
  - octreotide(30ug/kg/day)
  - Hydrocortisone
- what next?
  - Role of genetic studies
  - Indication for surgery
  - PET Scan??

Congenital Hyperinsulinism Infancy

- CHI is a heterogenous 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

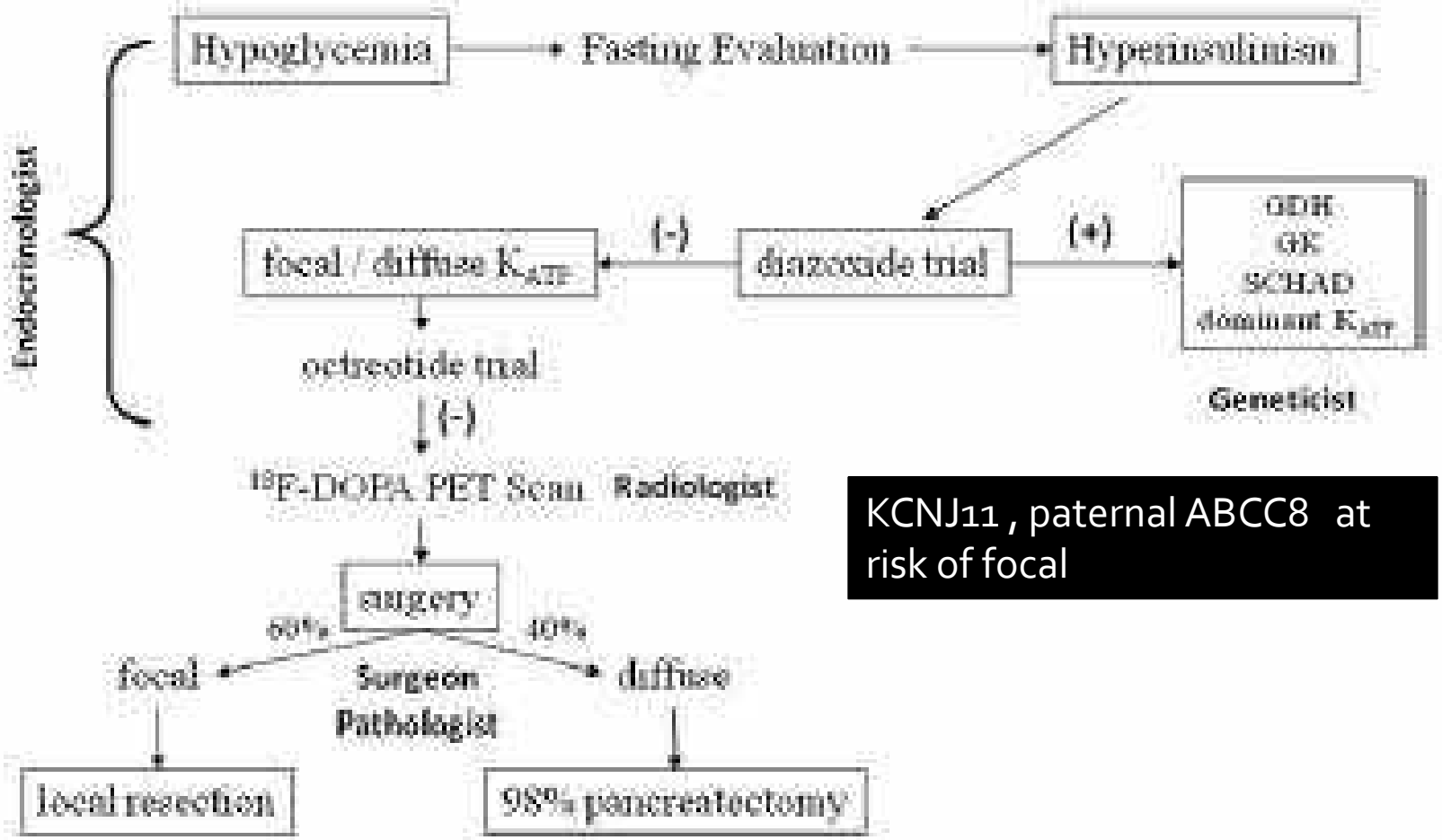
N/N
Asymptomatic



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

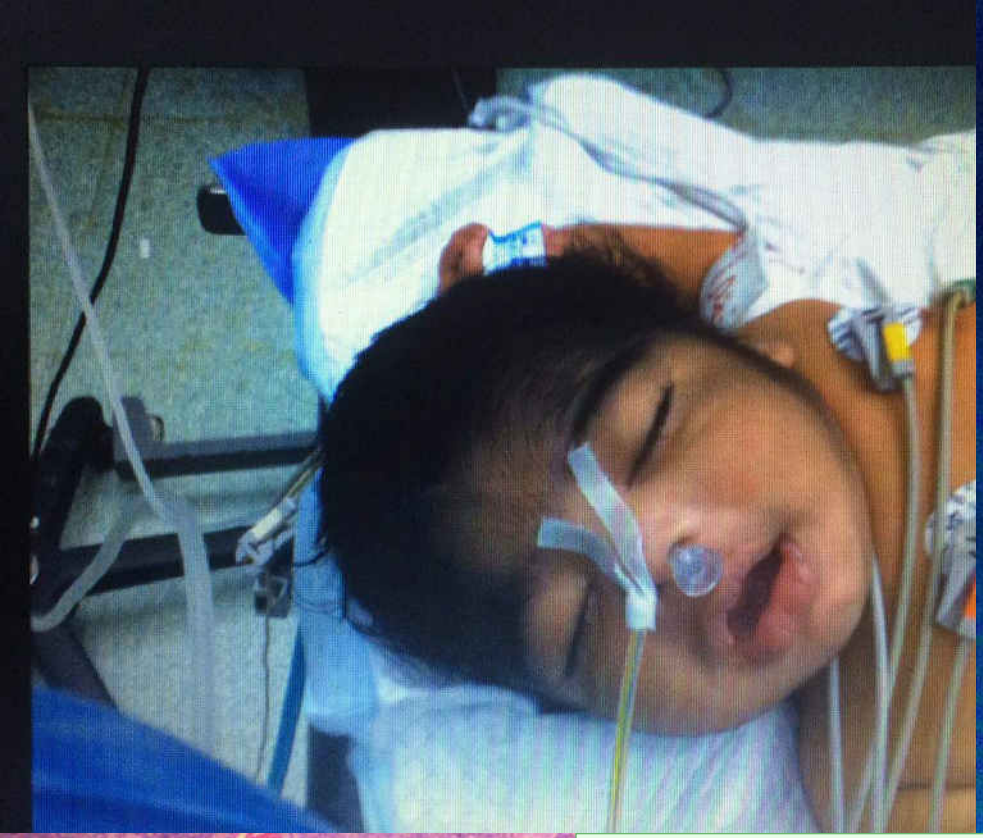
M/N, 3.5kg, CHI .
Gene-ABCC8
DNA-C.4253G>A ,Protein-(Arg1418His)
Missense mutation

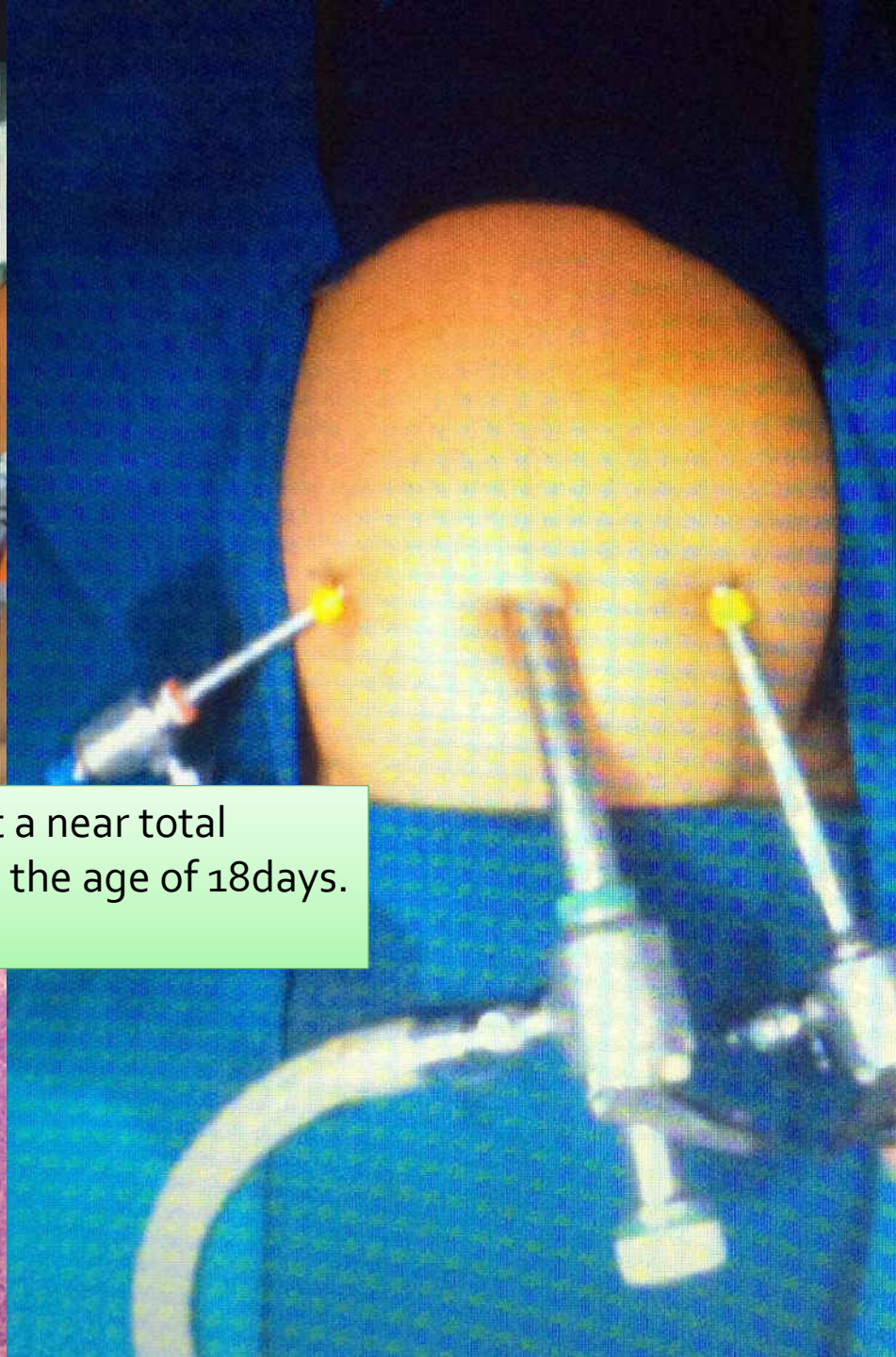
SCAN

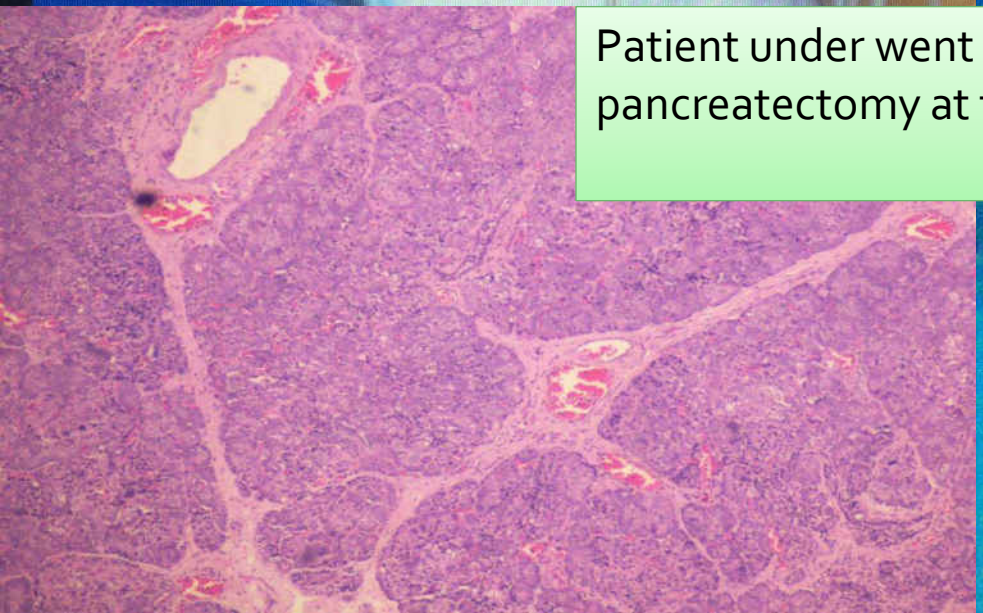


KCNJ11 , paternal ABCC8 at risk of focal

Seminars in Pediatric Surgery (2011) 20, 32-37







Patient under went a near total pancreatectomy at the age of 18days.

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 μg 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 μg/kg/d
Day 8-14	Evaluate effectiveness of octreotide with fasting test while awaiting transfer of patient

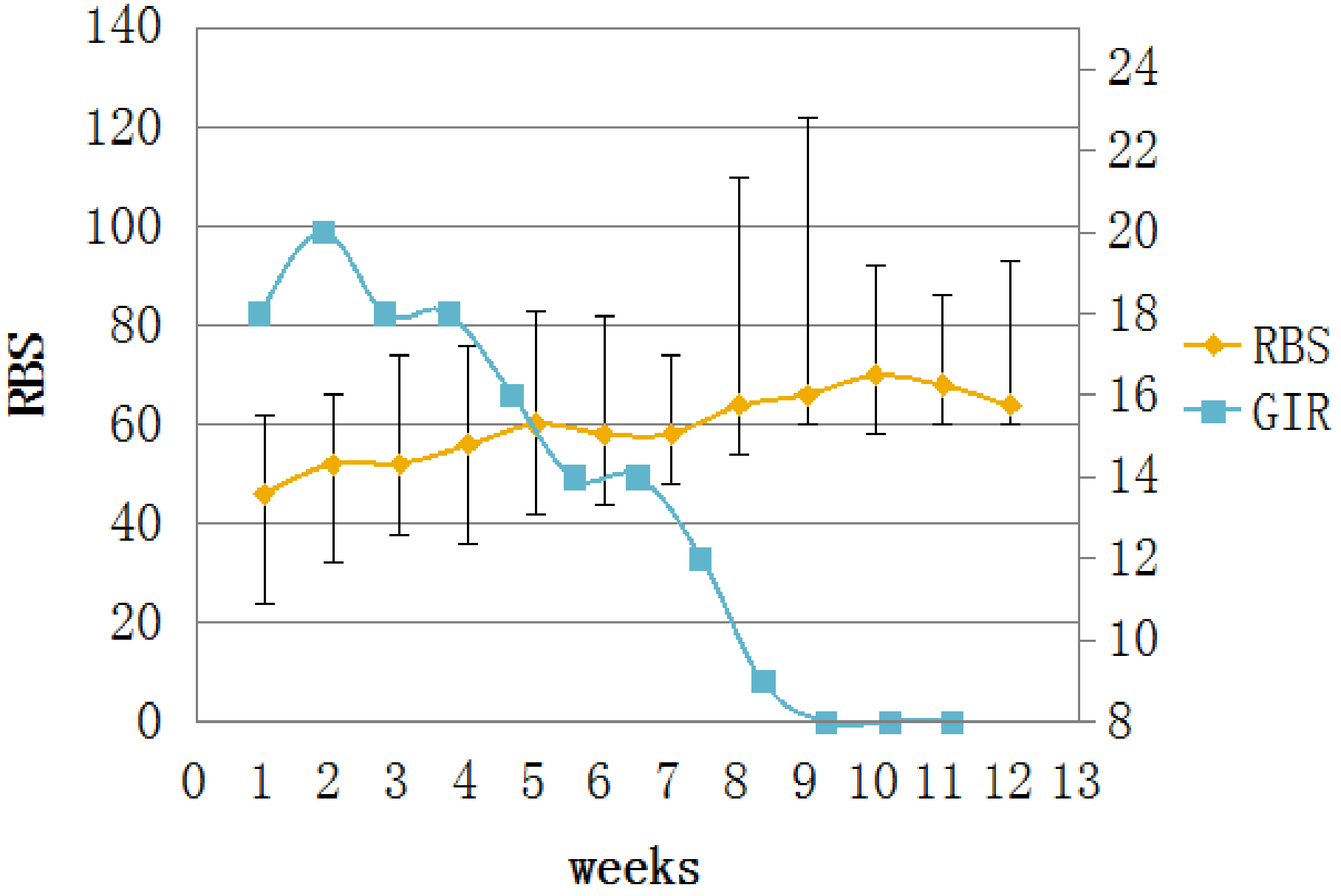
Pancreatectomy

- Post-operative infant remain hypoglycemic, even after diazoxide, octreotide and nifedipne (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 0.5mg/kg/day and subsequently it was increased to 1mg/kg/day.
- Gradually IV dextrose infusion was tapered and baby achieved normal blood sugar levels with oral feed(180ml/kg/day) and medications.

Senthil seniappan NEJM 2014


RBS
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0 1 2 3 4 5 6 7 8 9 10 11 12 13
weeks
RBS
GIR

Sirolimus

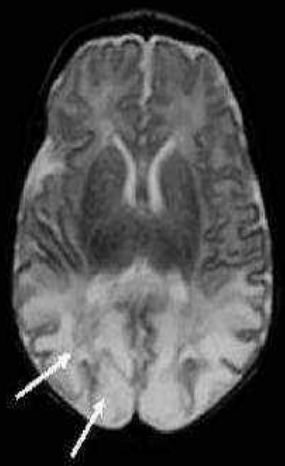
- A possible mechanism of betacell hyperplasia in CHI involves constitutive activation of mTOR pathway
- The mechanisms of action of sirolimus in hyperinsulinemic hypoglycemia has not fully understood but probably the effect on betacell mass is achieved **through inhibition of mTOR complex1(mTORC1) pathway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

Case

- 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 didnot notice any major side effects to sirolimus and development of child was appropriate for age.

Follow up & Outcome

- 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 etal, 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 perisistent hypoglycemia
- Development follow up
- **Method of screening and treatment of transient hypoglycemia need more studies**