



# Congenital Hyperinsulinism

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Neonatal Study Day

4 February 2020

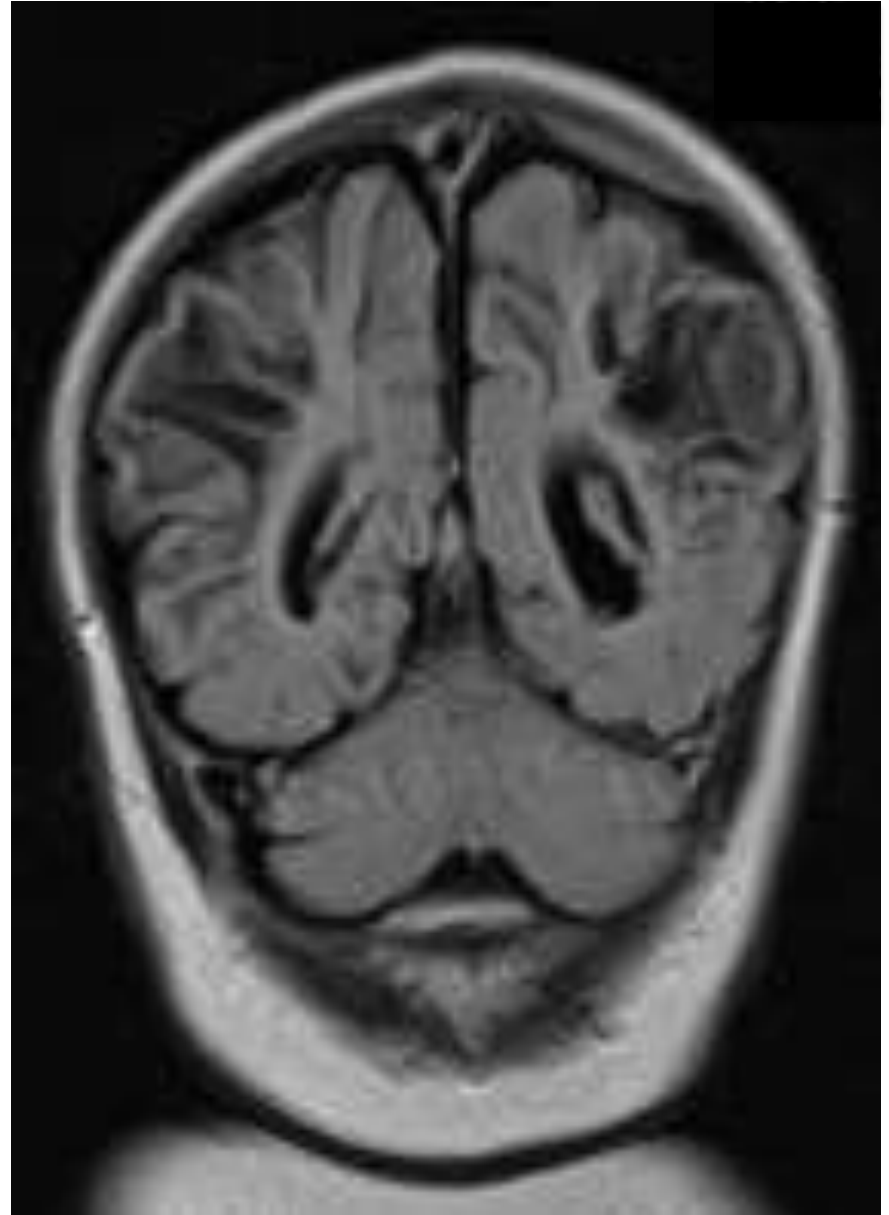
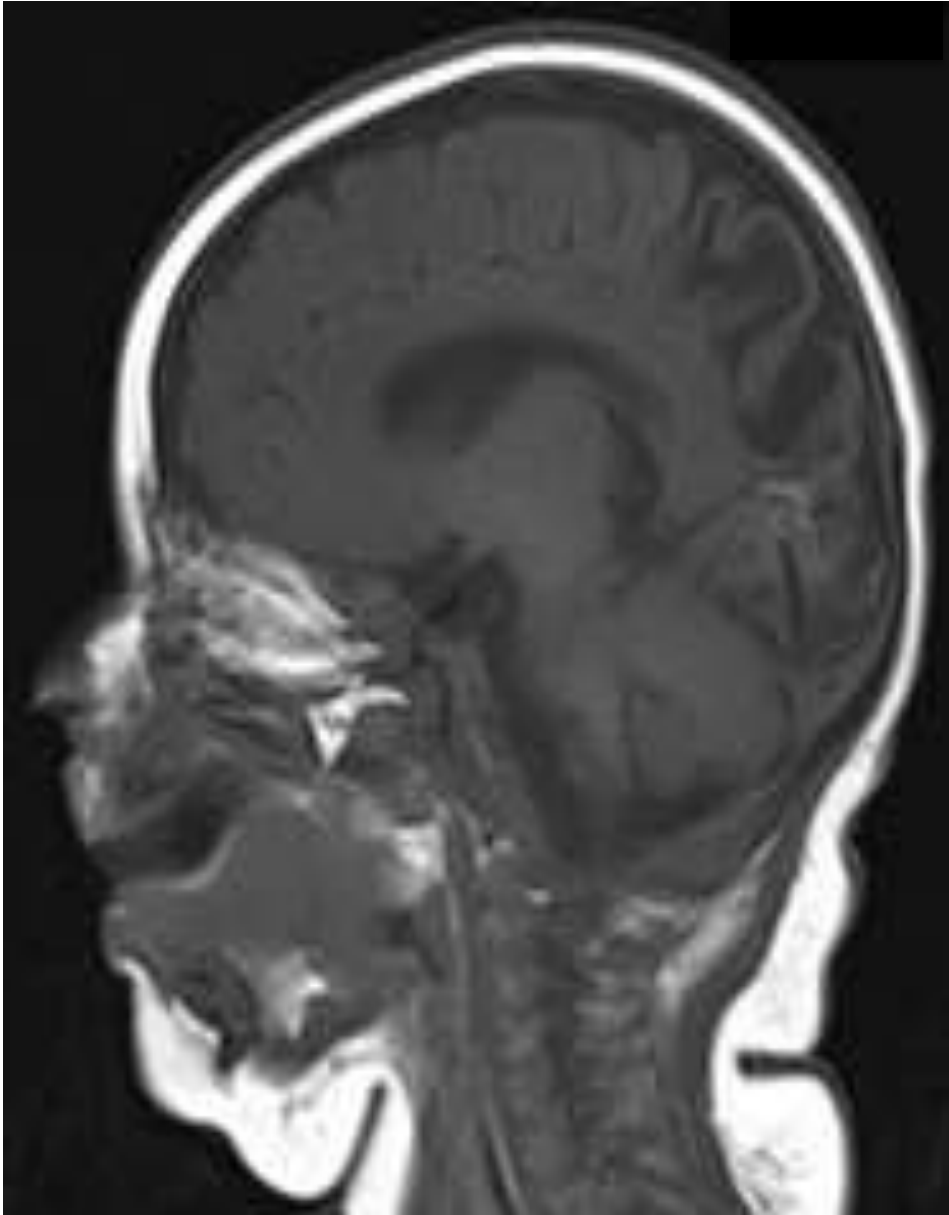
# Outline

- Diagnosis of Congenital Hyperinsulinism (CHI)
- Forms of CHI
  - Transient and Persistent
- Management
  - Initial management
  - Medications and side effects
  - Focal and Diffuse CHI
- Neurodevelopmental Outcomes
- Case presentation

# Congenital Hyperinsulinism (CHI)

- Most **frequent** cause of persistent and severe hypoglycaemia in infancy
- **Dysregulated, inappropriate and excessive insulin secretion**, independent of blood glucose levels
- **Hypoketotic hypoglycaemia** → High risk of irreversible **brain damage** (40%)

# Irreversible Brain Damage



# Diagnosis of CHI

# Diagnosis of CHI

**Evidence of excess insulin action at the time of hypoglycaemia ( $\leq 2.6$  mmol/L)**

- Non-suppressed insulin or C-peptide
- $\downarrow$  ketones (beta-hydroxybutyrate),  $\downarrow$  FFA
- Glycaemic response to glucagon ( $>1.7$  mmol/L)
- Increased glucose requirement (glucose infusion rate  $> 8$  mg/kg/min)

# Biochemical features of CHI

- Insulin not necessarily detectable at time of hypoglycaemia in patients with CHI
- C-peptide can increase the sensitivity for diagnosis of CHI but not 100%
- Ketones
  - Ketogenesis suppressed during transitional neonatal hypoglycaemia

# Forms of CHI

# Forms of CHI

## Transient forms

- Perinatal stress
- Maternal diabetes

## Persistent forms

- Genetic CHI
- Syndromic forms of CHI
- Persistent, no identified cause

# Transient CHI

- Common, estimated 10% of SGA infants
- Diazoxide-responsive, variable duration
- Risk factors:
  - IUGR/SGA
  - Pre-eclampsia/maternal hypertension
  - Perinatal asphyxia
  - Prematurity
  - Haemolytic disease of the newborn
  - Maternal labetolol, IV dextrose

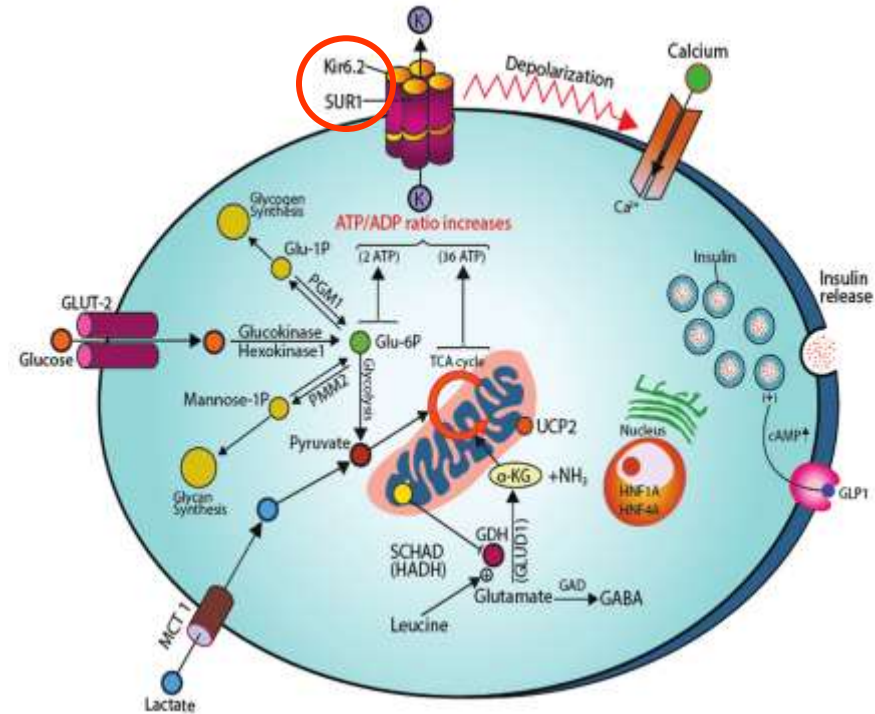
# Persistent CHI

- Genetic cause in 45-55%

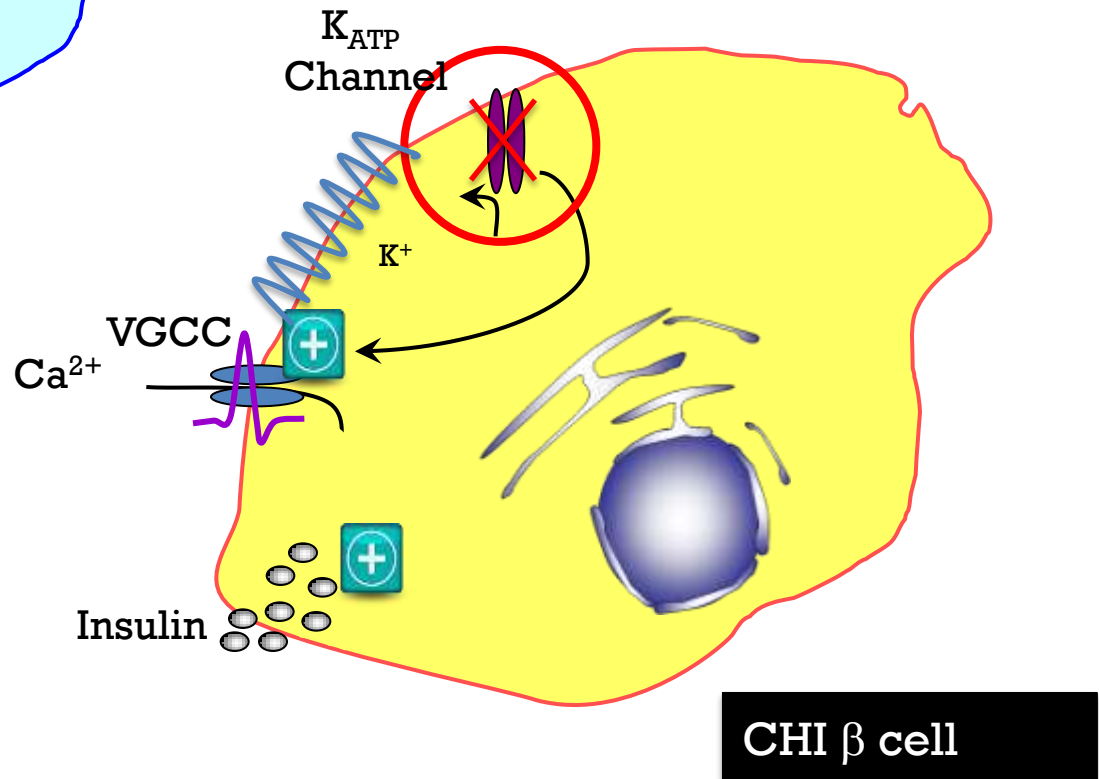
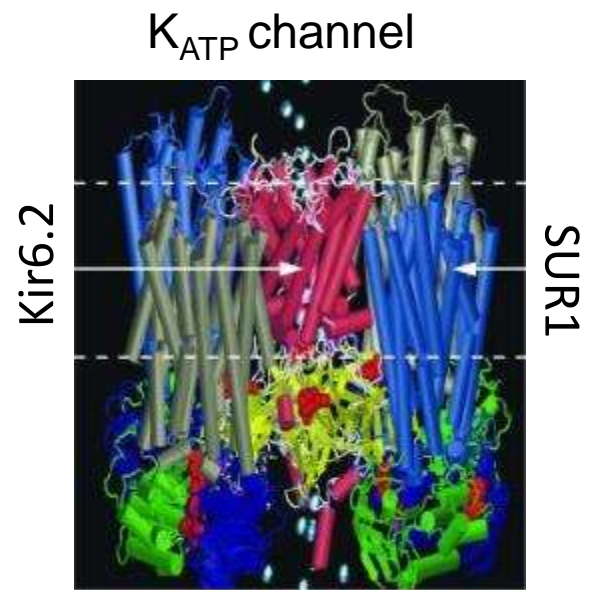
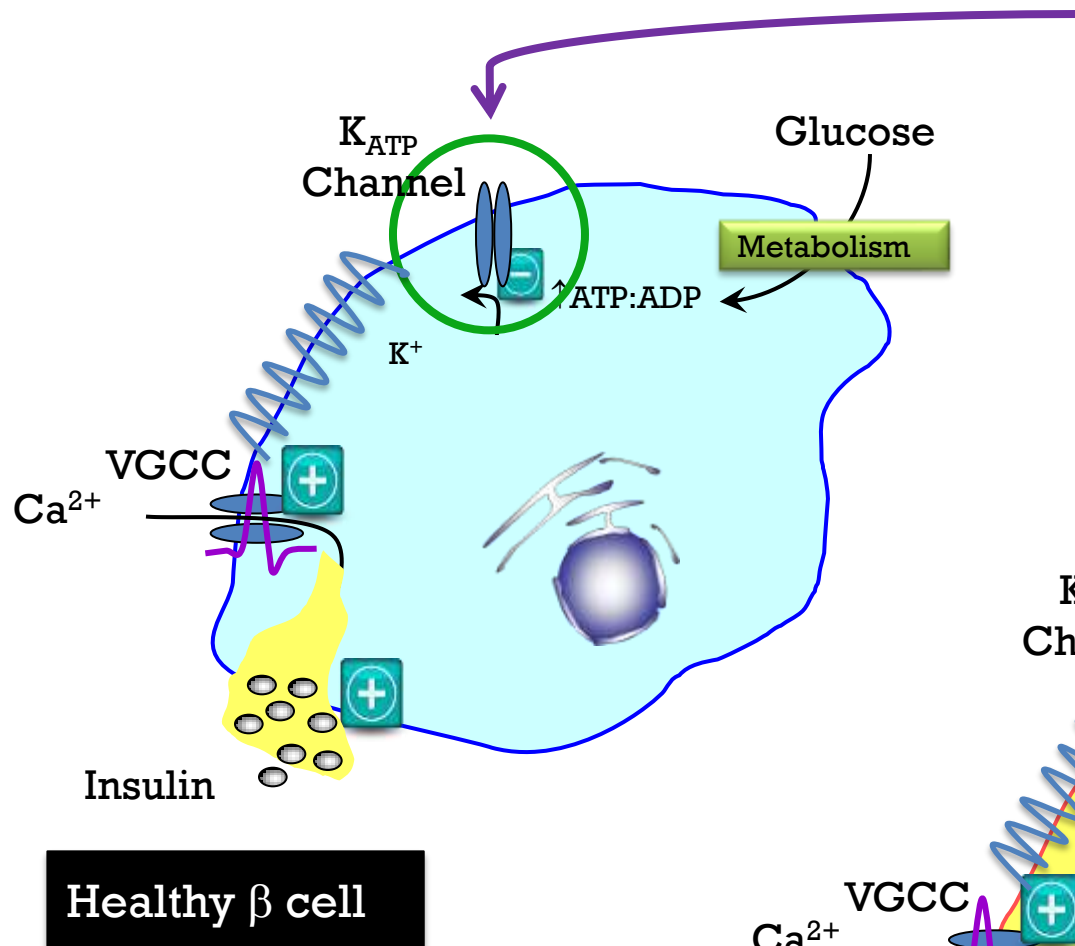
- *ABCC8* and *KCNJ11* mutations

- Others:

*GLUD1, GCK, HADH, SLC16A1, HNF1A, HNF4A, UCP2, HK1, PMM2, PGM1, FOXA2, CACNA1D, MCT1*



Demirbilek H, 2017



# K<sub>ATP</sub> Channel Mutations

- Most common forms of genetic CHI
  - Nearly 90% of diazoxide-unresponsive cases

- Homozygous
- Compound Heterozygous
- Maternal heterozygous



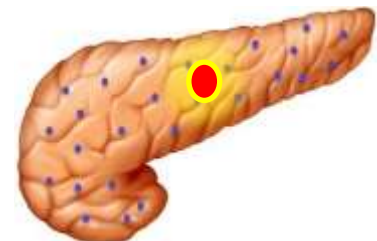
## Diffuse CHI



- Paternally heterozygous



## Focal CHI



# Syndromic Forms of CHI

<b>Beckwith-Wiedemann Syndrome</b>	Hypoglycaemia in 30-60% Usually transient, severe in up to 20% Pre and postnatal overgrowth, organomegaly, hemihypertrophy, risk of embryonal tumors
<b>Kabuki Syndrome</b>	HI can be presenting feature, DZX-responsive Distinctive facial appearance, short stature, skeletal abnormalities, developmental delay, heart defects
<b>Turner Syndrome</b>	Mosaic and non-Mosaic Variable severity
<b>Sotos Syndrome</b>	Pre and postnatal overgrowth, dolichocephaly, distinctive facial features, developmental delay
<b>Costello Syndrome</b>	Short stature, developmental delay, coarse facial features, papillomata, joint laxity, cardiac defects, tumor risk
<b>FOXA2</b>	Mild CHI Congenital hypopituitarism

# Initial Management

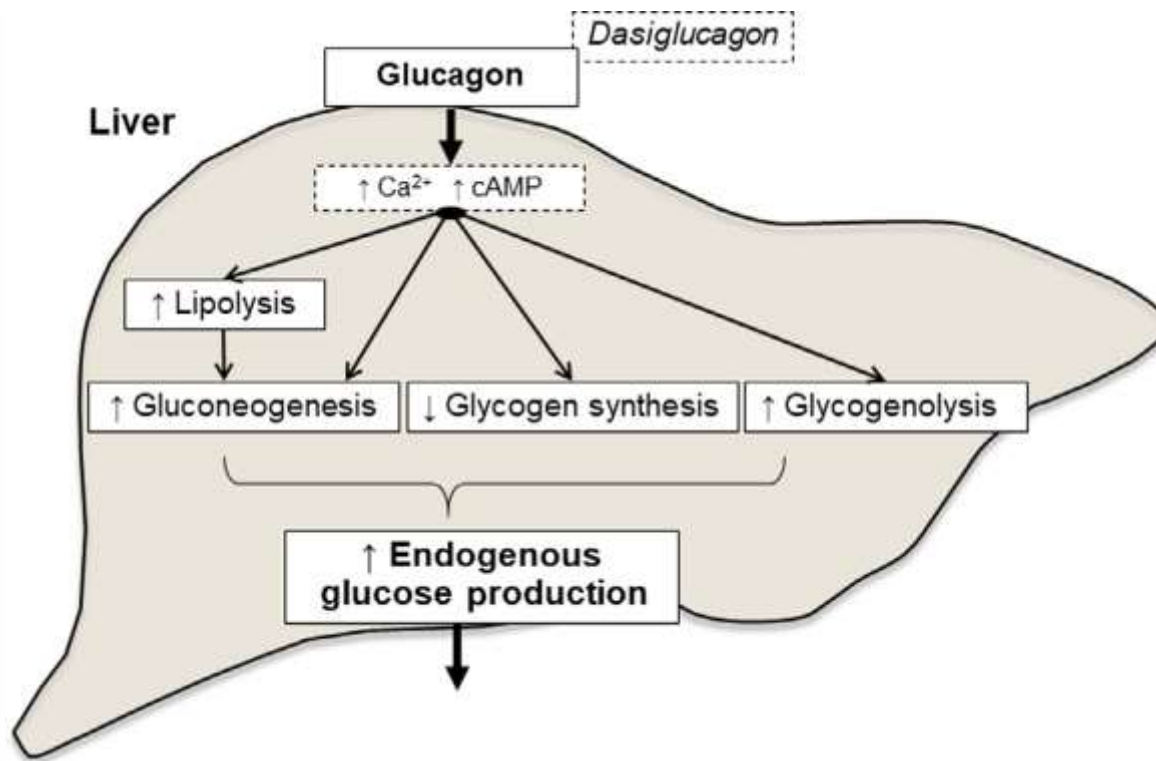
# Initial Management of CHI

- Increase **glucose** intake (enteral or IV)
- Increase endogenous glucose production: **glucagon**
- Reduction of insulin secretion: **diazoxide**

# Glucagon

- Emergency treatment (IM) or
- Initial glycaemic stability (SC/IV)

Necrolytic migratory erythema



# Initial Management of CHI

- Increase glucose intake (enteral or IV)
- Increase endogenous glucose production: glucagon
- **Reduction of insulin secretion:**

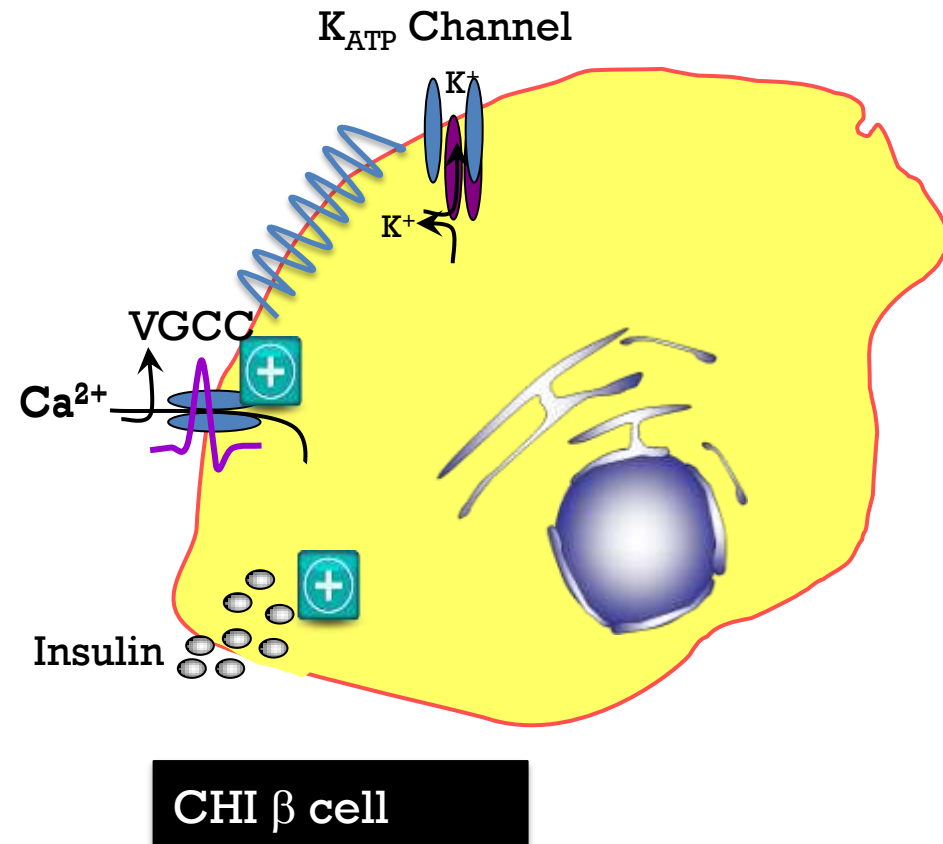
- **Diazoxide**



- First line medication
- Response to diazoxide is key to guide further management

- Target blood glucose  $>3.5$  mmol/L
- Close glucose monitoring
- Fluid volume
- Echocardiogram

# Diazoxide



- Effective oral treatment
- First choice
- Dosing: 5-15 mg/kg/day
- Concurrent chlorothiazide

## Caution:

Fluid overload  
Thrombocytopaenia  
Pulmonary  
Hypertension

# Diazoxide side effects



# Diazoxide – pericardial effusion



# Diazoxide – Pulmonary Hypertension

- N=177 CHI patients, at four centres
- 13/177 (7.3%) developed PHT
- Complete withdrawal led to resolution
- **Risk factors:**
  - Congenital Heart Disease
  - Total fluid volume > 130 ml/kg/day

# Diazoxide

- Echocardiogram
- Fluid volume
  - Total fluids no greater than 150 ml/kg/day (IV + oral + medications & infusions)
- Concurrent diuretic administration
  - Chlorothiazide
  - Monitoring for ↓ Na, ↓ K
- Weaning of IV fluids/titrating enteral feeds

**NEW CHI ADVICE LETTER**

**Date:**

To Whom It May Concern,

**Child's Name:**

**DOB:**

**NHS Number:**

**Documented Current Weight:** 2.9 Kg (as per your communication)

Many thanks for your referral. As per advice given, the recommended plan for monitoring is as follows;

**Medications**

Diazoxide 5 mg/kg/day (in 3 divided doses) ie. 5 mg per dose

Chlorthiazide 7 mg/kg/day (in 2 divided doses) ie. 10 mg per dose

*Where possible we recommend the preparation of Diazoxide Proglycem (50mg/ml).*

**Fluid Management**

Fluid retention is one of the side effects of Diazoxide. Therefore please give a maximum volume of 150 mls/kg/day and monitor closely for any signs of fluid retention.

Please monitor:

U+E Bloods	Daily
Weight	Daily
Input/Output chart	Daily

**Blood Glucose Monitoring**

Please monitor blood glucose levels every 2 hours.

Please do not hesitate to contact our team with any problems on 0161 276 1234 for the on-call Endocrine registrar (bleep 1630) or consultant via hospital switchboard. Please update us in 24-48 hours after starting Diazoxide and inform us 24 hours before they are due to be discharged. Any changes to the above recommended medications should be discussed with one of our team members.

Once blood glucose levels are stabilised and the child is discharged home they will be contacted by one of our clinical nurse specialists.

As detailed in the attached Discharge Checklist, they will need to go home with a Blood Glucose monitor and Hypoglycaemia management plan, and we will require a referral letter





# Manchester University

## NHS Foundation Trust

### **Congenital Hyperinsulinism: DGH Discharge Check List**

	Done ✓	To be completed by
Home BM training for parents and home BM monitor provided		DGH
Hypoglycaemia Flowsheet reviewed with parents (see appendix 1)		DGH
Six hour safety fast completed (see appendix 2 for proforma)		DGH
TTO for medications including glucogel for hypoglycaemia rescue		DGH
Open access at local hospital		DGH
Contact numbers of CHI nurses provided to parents (0161 701 2460/0518)		
<b>Referral sent <u>BEFORE</u> discharge to ensure a 4-6 week post-discharge outpatient visit can be arranged in Manchester*</b> <b>Fax 0161 701 1631</b> <b>Email: <a href="mailto:jacqueline.dignan@nhs.net">jacqueline.dignan@nhs.net</a></b> <b>Please include telephone numbers of parents</b>		DGH

\*Badger summary acceptable **if** contains relevant information regarding diagnosis and management of CHI (e.g. presentation, hyposcreen results, acute management and discharge treatment) and other major medical issues

# Pre-Discharge Safety Fast

## Appendix 2

### **Six-hour safety fast for infants with Congenital Hyperinsulinism (CHI) prior to discharge**

It is essential that babies with CHI complete a 6-hour safety fast prior to discharge to ensure they are safe at home. This should be done even if they are not on any treatment currently for CHI but have had raised insulin in the presence of hypoglycaemia.

Prior to undertaking the fast the baby should be on at least 3 hourly feeds and preferably 4 hourly feeds. A feed should be omitted and blood glucose levels checked hourly as per the table below. If at any time during the fast the blood glucose levels **drop below 3.5mmol/L**, then the fast should be stopped and the baby should be fed. If this occurs before the 6-hour time frame, the fast will be deemed to be failed and further advice should be sought from the endocrine team at Royal Manchester Children's Hospital before the baby is allowed home.

**Name:**

**DOB:**

**NHS number:**

**Medications and supplements if applicable:**

**Feeds (formula/EBM, supplementation if application, frequency):**

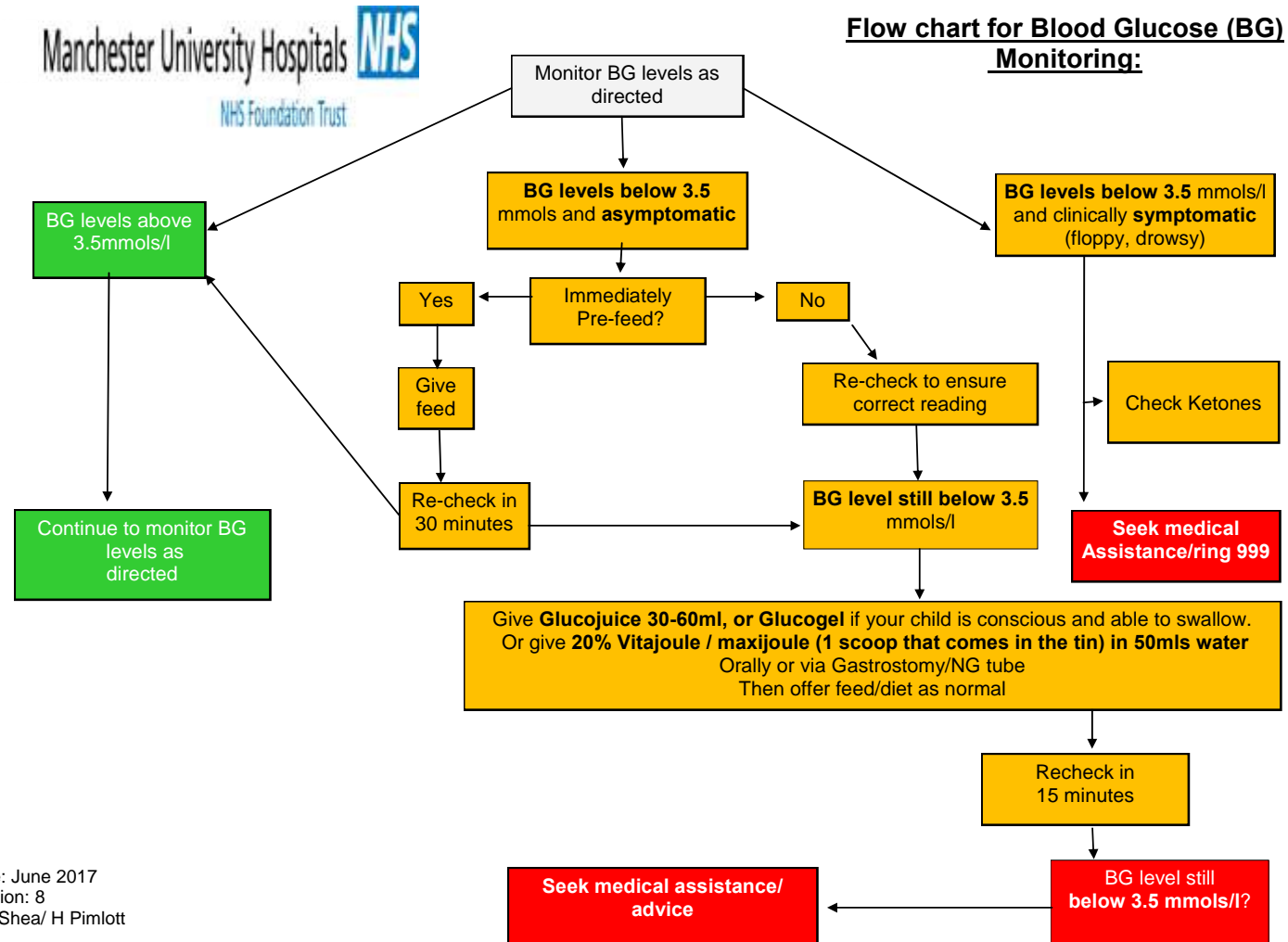
**Date fast performed:**

<u>Time since last feed</u>	3 hours	4 hours	5 hours	6 hours	Post feed
Blood Glucose (mmol/L)					

Please fax the results to the Endocrine Team at Royal Manchester Children's Hospital on 0161 701 1631 for the attention of the CHI fellow or Endocrine Registrar.

# CHI Hypoglycaemia Home Management

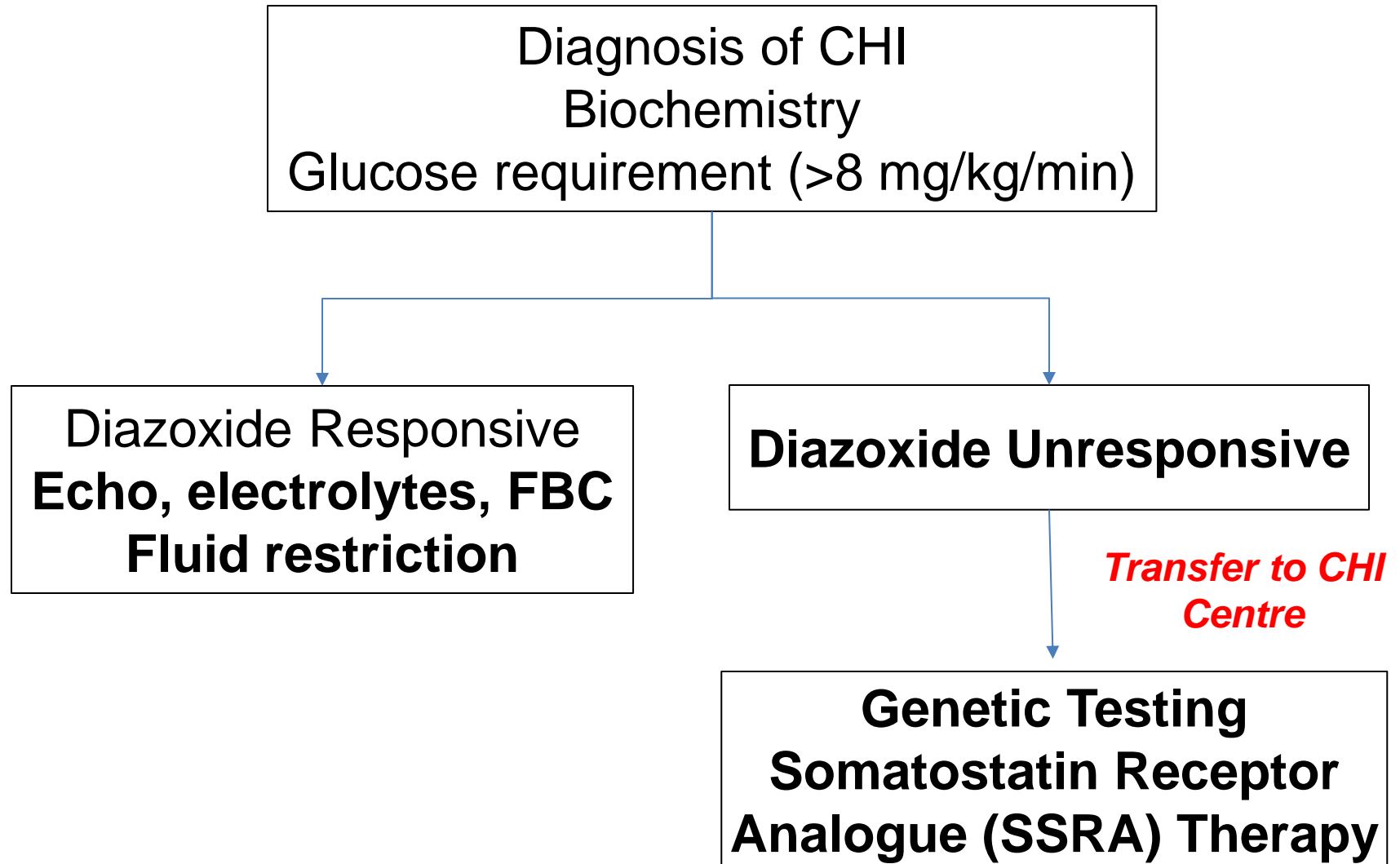
## Appendix 1

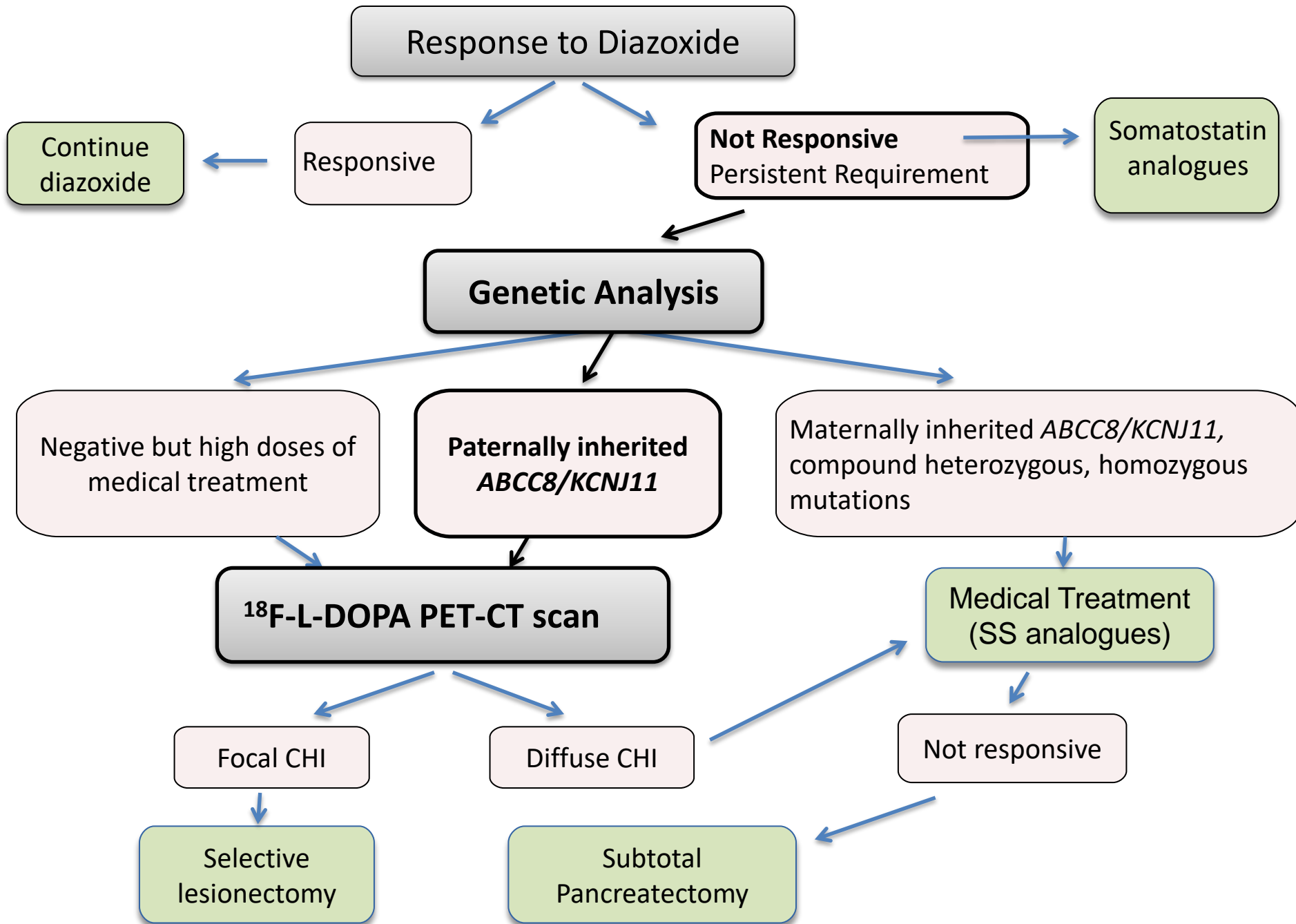


# Outpatient Follow Up

- Outpatient visit at RMCH 4-6 weeks after DGH discharge
  - All patients on diazoxide
- Telephone contact between CHI Nurses and families within 1<sup>st</sup> week after discharge
- “Self-wean” vs. active reduction
- Genetic testing if persistent

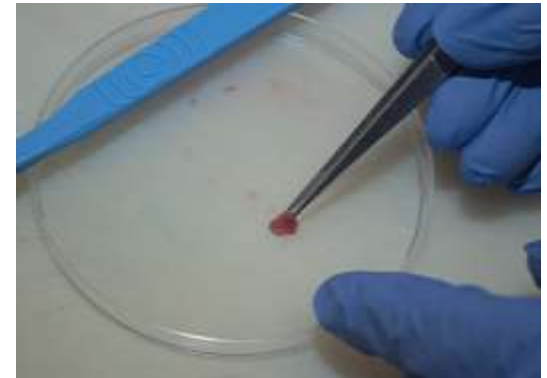
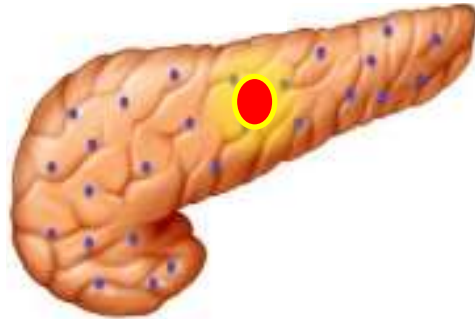
# Approach to Management





# $K_{ATP}$ Mutations – Focal CHI

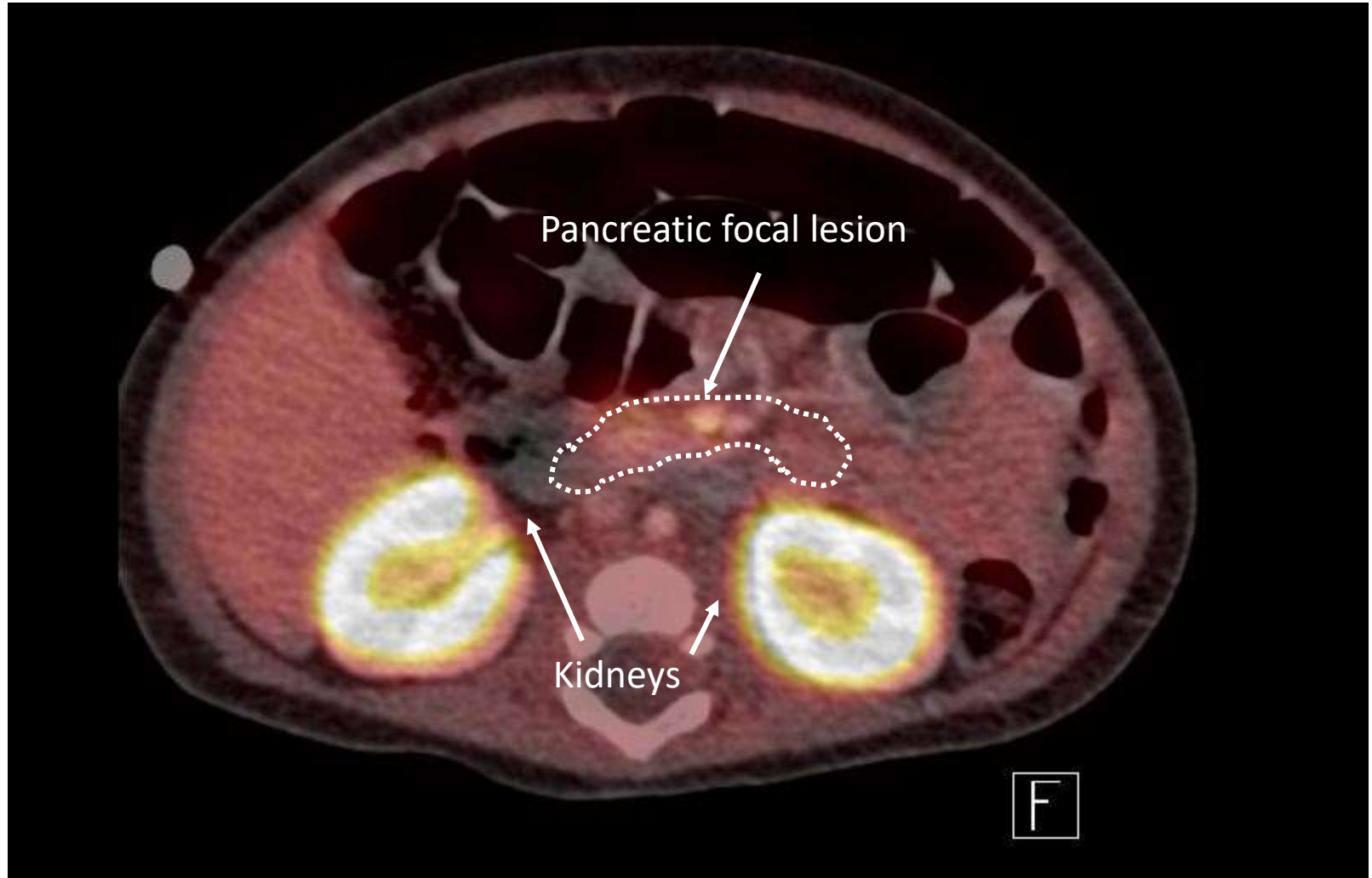
Focal CHI



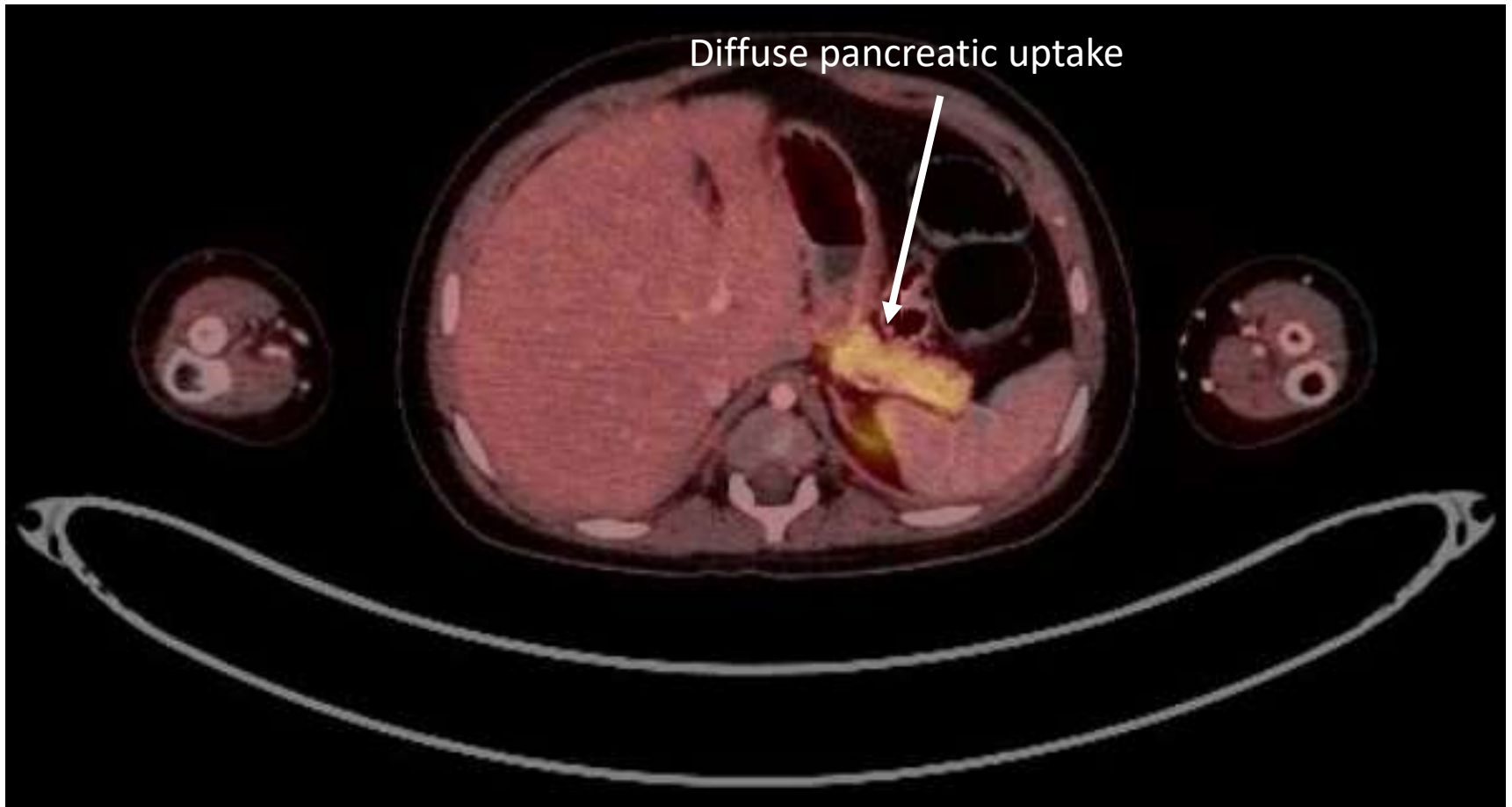
# $K_{ATP}$ Mutations – Focal Disease

- Often later onset: 72% present at 6-7 weeks
- **$^{18}\text{F}$  DOPA PET CT** scan: presence and localization of focal lesion
- Treatment response
  - Diazoxide and octreotide unresponsive
- **Surgery** curative in the majority of cases

# Focal CHI on $^{18}\text{F}$ -L-DOPA PET-CT



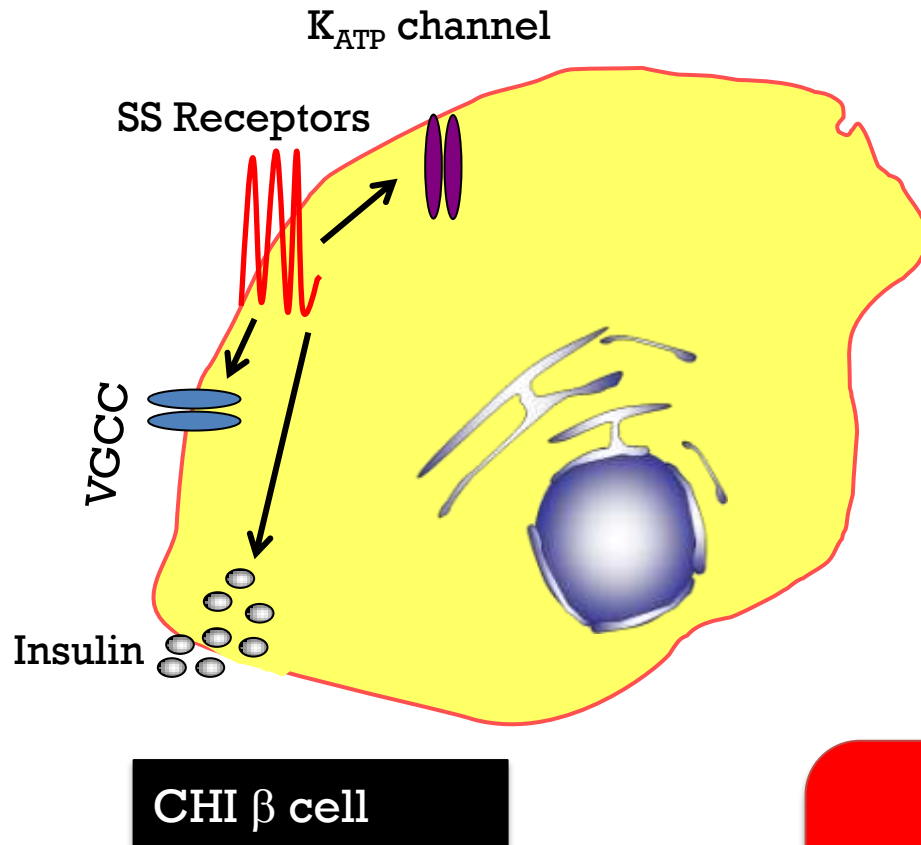
# Diffuse CHI on $^{18}\text{F}$ -L-DOPA-PET-CT



# $K_{ATP}$ Mutations – Diffuse Disease

- Most **severe** of monogenic CHI forms
- Presentation in **early** neonatal period
- 65-87% - **large** for gestational age
- Treatment Response
  - Homozygous and Compound Heterozygous mutations
  - Dominant mutations

# Somatostatin analogues



Octreotide

LAR-octreotide

Lanreotide

Second line  
IV or SC treatment

Variable Response  
Tachyphylaxis

Caution:  
Hepatitis  
Necrotising Enterocolitis

# The challenge of Diffuse CHI

- Diazoxide, somatostatin analogues

Not always effective  
Serious side effects

- Subtotal pancreatectomy

Persistent CHI  
Diabetes Mellitus  
Exocrine insufficiency

Future Therapies

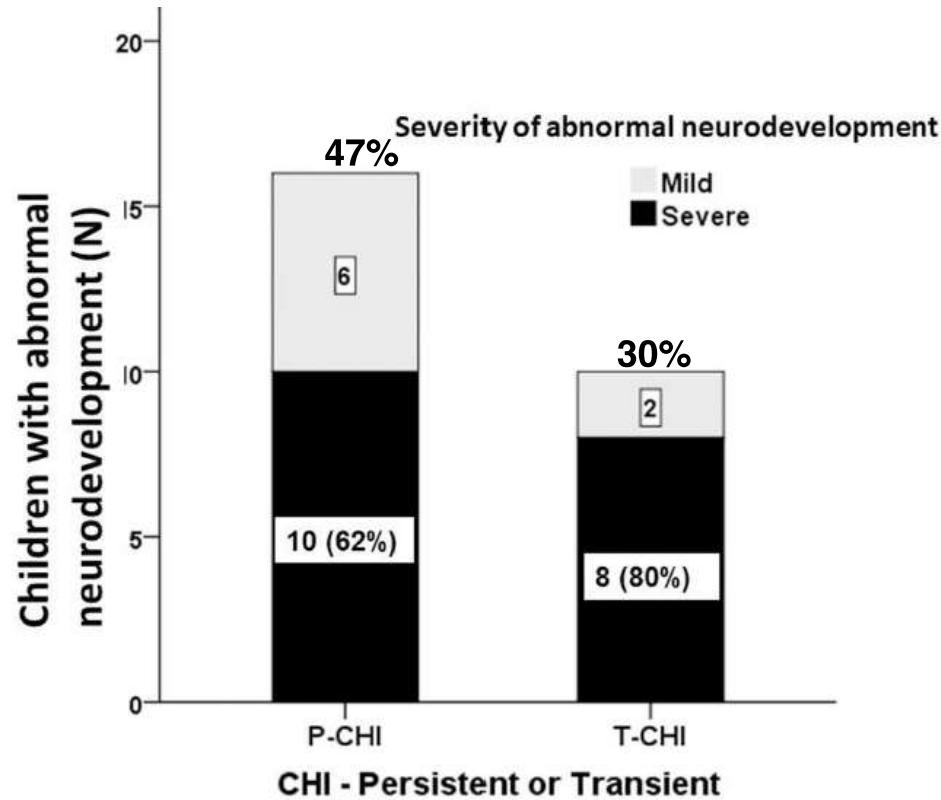
- High risk of irreversible brain damage (40%)

# Neurodevelopmental Outcomes

# Neurodevelopmental Outcomes

- Neurodevelopmental impairment in **26-48%**
- **Broad range** of issues:
  - intellectual disability, epilepsy, blindness, motor problems, speech, behavioural issues
- Rates have not changed much despite advances in molecular genetics, imaging and therapeutic approaches

# Neurodevelopmental Outcomes



Avatapalle, *Front Endocrinol*, 2013

are common both in transient and permanent CHI

# Conclusions

- **Heterogeneous** aetiology, clinical manifestations and response to treatment
- First line treatment with **diazoxide** requires careful monitoring
- Significant rate of **neurodevelopmental abnormalities** in both transient and persistent cases

# **CHI Case Presentation**

**Dr West**



# Case Presentation

Rebecca West  
ST6 Paediatrics  
Endocrinology,  
RMCH

# Initial Presentation

## Background

- Presented 30 hours of age in Galway, jittery and lethargic
- Blood glucose 0.5mmol/L
- Required increasing concentrations of dextrose so transferred to Dublin.

# Admission at Dublin

## Repeated hypoglycaemic episodes

- Initial GIR 15.4mg/kg/min
- **CHI** confirmed
- Unresponsive to increasing doses chlorthiazide and diazoxide.
- Octerotide commenced day 16
- High GIR persisted despite increasing doses of octreotide

Hypoglycaemia screen	<ul style="list-style-type: none"><li>• <b>Insulin</b> <b>140pmol/L</b>, with glucose of 1.8mmol/L</li><li>• C-peptide 741pmol/L cortisol 741pmol/L</li></ul>
Genetics	<ul style="list-style-type: none"><li>• Paternally inherited KCNJ11 mutation</li></ul>
ECHO	<ul style="list-style-type: none"><li>• Normal.</li></ul>

# At RMCH

18 F-DOPA PET CT initial report showed **diffuse** uptake of tracer.

Recommenced on diazoxide, poor response and symptoms of fluid overload.



- Formal PET-CT report showed a **focal lesion**, mild increased uptake in body of pancreas.

- Octreotide weaned, glucagon infusion up to 11mcg/kg/min

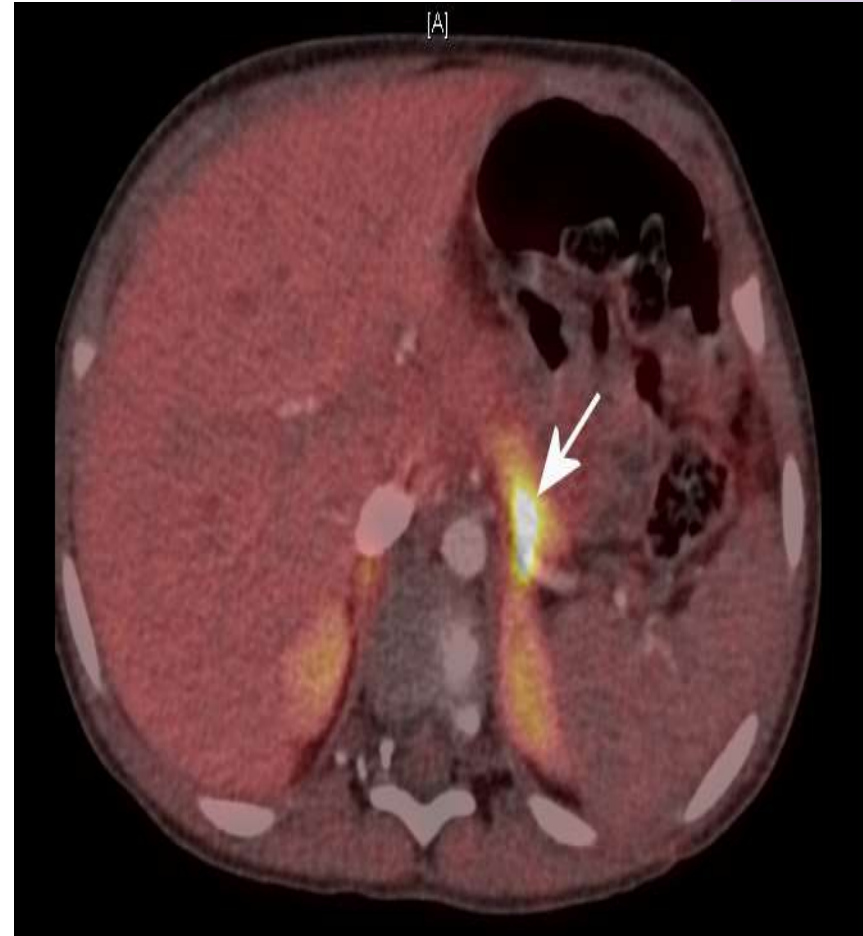


Laparotomy, focal lesion identified, **focal lesionectomy** and PEG insertion



Hypoglycaemia resolved and passed 6 hour safety fast.

# PET-CT



# Other Issues

- Oral aversion, requiring NG then PEG feeds.
  - Venous access – required multiple central lines.
  - Prophylactic Enoxaparin
  - Red Cell Transfusion
  - Staph aureus on gastrostomy swab
- 
- GOR
  - Delayed immunisations

# Progress

At discharge home, aged 4 months

- Off all CHI medications
- 100-120ml EBM/standard formula every 3 hours via bottle/PEG
- Parents appropriately trained
- Neuro-developmentally appropriate
- Open access to local hospital and OP follow up with NORCHI.

?

Thank you  
to Dr Maria Salomon Estebanez and Prof Indi Banerjee