Congenital Hyperinsulinism…Current Therapies

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Congenital hyperinsulinism (CHI)

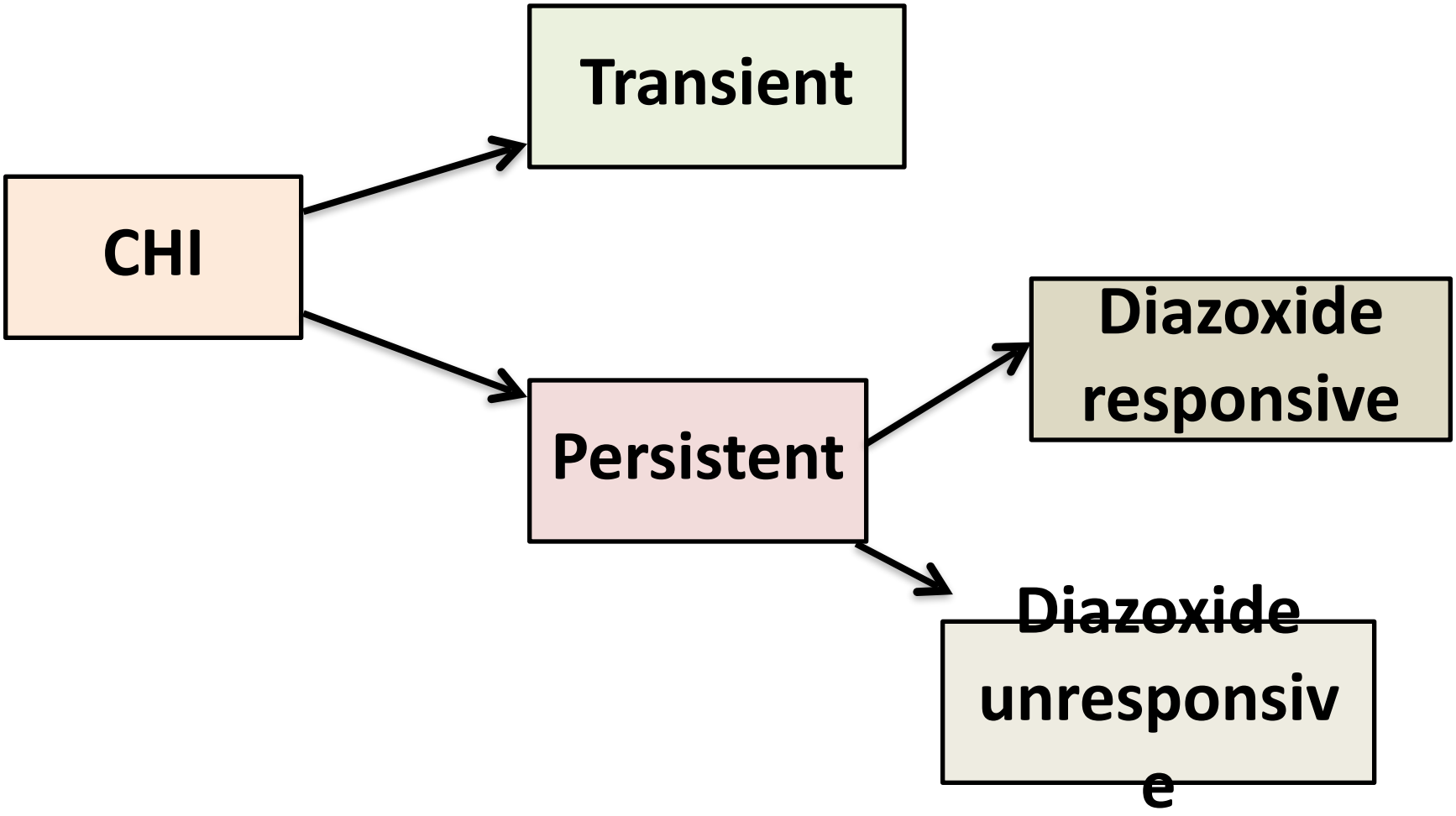
- Commonest cause of recurrent & persistent hypoglycaemia in infants & children

- Presentation – neonatal hypoglycaemia, seizures/ hypoglycaemia in infancy/later childhood, developmental delay

Diagnosis

- Glucose Infusion Rate **> 8 mg/kg/min**
- Inappropriately detectable Insulin/C-peptide during hypoglycaemia
- Inappropriately **low free fatty acid and ketone bodies** during hypoglycaemia

CHI


CHI
Transient
Persistent
Diazoxide responsive
Diazoxide unresponsive

Transient CHI

- Maternal diabetes mellitus
- Perinatal hypoxia
- IUGR, Prematurity
- Maternal drugs (β-blockers)
- Syndromes - Beckwith-Wiedemann

- Variable duration of hypo

Neurodevelopmental Outcomes

frontiers in ENDOCRINOLOGY

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Abnormal neurodevelopmental outcomes are common in children with transient congenital hyperinsulinism

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Introduction: Neuroglycopenia is recognized to be associated with abnormal neurode velopmental outcomes in 26–44% of children with persistent congenital hyperinsulinism (P-CHI). The prevalence of abnormal neurodevelopment in transient CHI (T-CHI) is no known. We have aimed to investigate abnormal neurodevelopment and associated fac

Medical Management

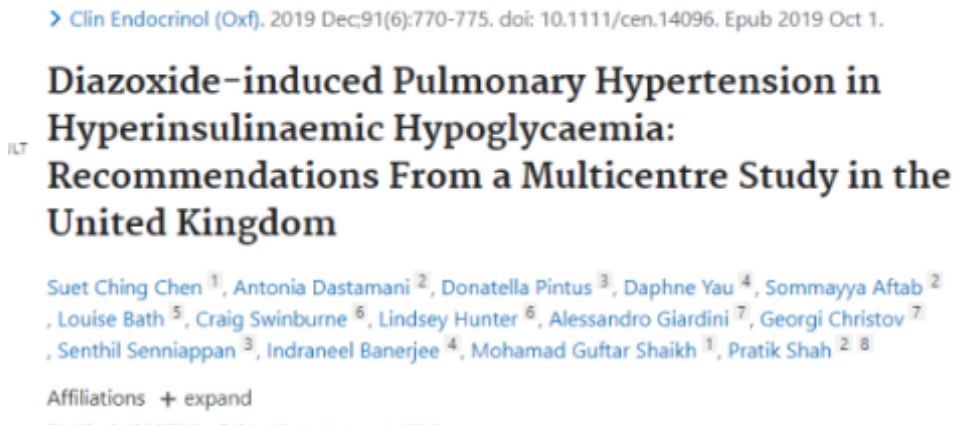
- Blood glucose stabilisation – intravenous high concentration dextrose infusion (central line)
- IV glucagon continuous infusion (5-20mcg/kg/hr)
- Regular monitoring – glucose, electrolytes
- Enteral feeds as tolerated…

Medical Management

- **Diazoxide** (fluids should be restricted to max 130-140ml/kg/day)
- Diazoxide dose range: 5-20mg/kg/day
- + Chlorothiazide BD (furosemide & spironolactone at higher doses)
- Baseline **Echocardiogram** (prior to diazoxide)

Side effects of Diazoxide

- Fluid retention, weight gain
- Hyponatremia
- Heart failure
- **Hypertrichosis**
- **Pulmonary hypertension**



> Clin Endocrinol (Oxf). 2019 Dec;91(6):770-775. doi: 10.1111/cen.14096. Epub 2019 Oct 1.

Diazoxide-induced Pulmonary Hypertension in Hyperinsulinaemic Hypoglycaemia: Recommendations From a Multicentre Study in the United Kingdom

Suet Ching Chen [1], Antonia Dastamani [2], Donatella Pintus [3], Daphne Yau [4], Sommayya Aftab [2], Louise Bath [5], Craig Swinburne [6], Lindsey Hunter [6], Alessandro Giardini [7], Georgi Christov [7], Senthil Senniappan [3], Indraneel Banerjee [4], Mohamad Guftar Shaikh [1], Pratik Shah [2 8]

Affiliations + expand

Diazoxide Responsive..

- Discharge home on diazoxide/diuretics
- Training for parents – glucose monitoring
- Clear ‘hypo plan’
- Glucogel (hypostop)
- **6-8 hours Safety ‘fast’**
- MDT support (specialist nurse, endocrinologist, dietician, speech/language therapist, psychologist)
- Ongoing follow up

Progress…

No response to Diazoxide (20mg/kg/day)

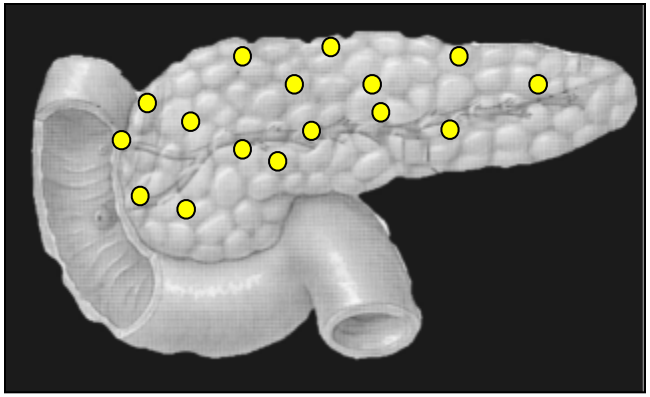
What Next?

Senniappan S, *Shanti B, James C, Hussain K. Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management. J Inherit Metab Dis. 2012 Jul;35(4)*

Histological subtypes

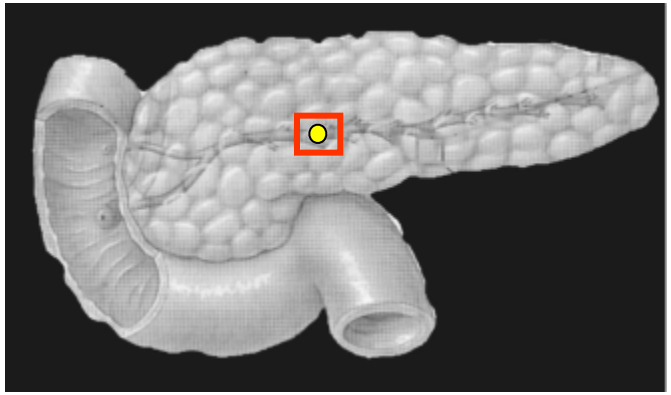
Diffuse disease

Histological abnormalities in beta cells throughout the pancreas



Focal disease

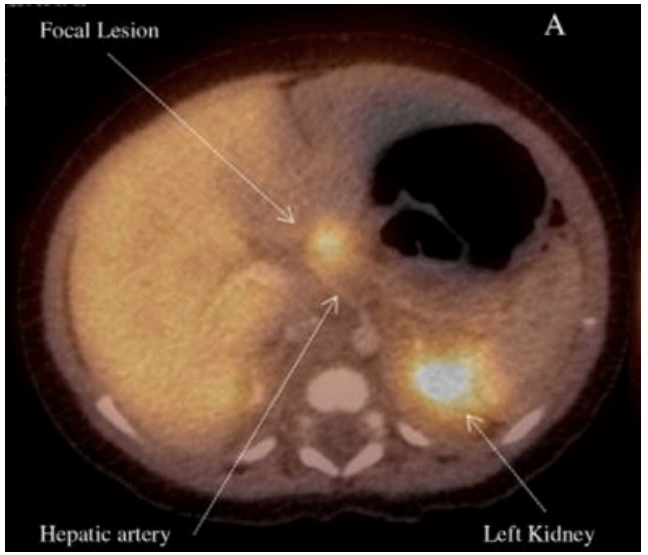
Focal islet-cell hyperplasia within the lesion, rest of the pancreas normal



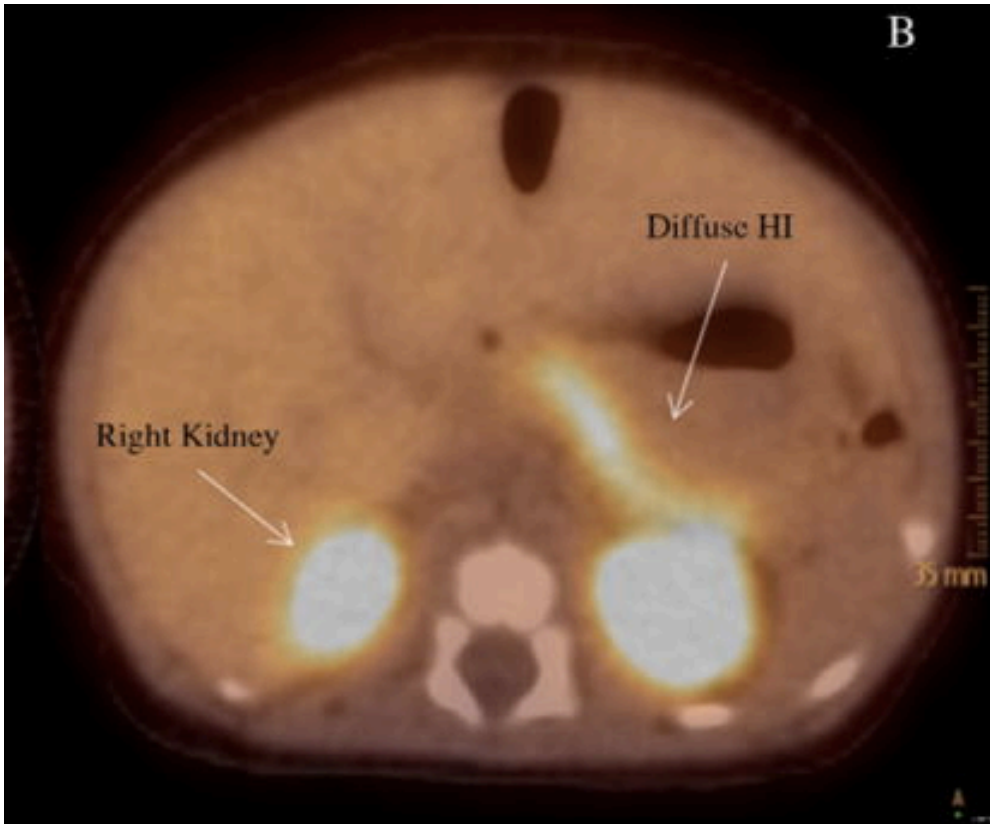
18F-DOPA-PET/CT

Focal CHI

- Paternal *ABCC8, KCNJ11* (heterozygous) mutation with somatic maternal loss of heterozygosity
- Usually <1cm diameter
- Not ‘insulinoma’
- Removal of focal lesion is curative



Diffuse disease



Medical Management

- Octreotide 6-8 hourly SC injections (5-40mcg/kg/day)
- Octreotide continuous SC infusion via pump
- Diet – high calorie, frequent or continuous feeds

Octreotide

- Tachyphylaxis
- Cholestasis & gall stones
- GI disturbances (usually transient)
- Growth Suppression
- TSH suppression
- **Necrotising Enterocolitis (NEC)**

Long-acting Somatostatin Analogues

- Selective binding affinity for **SSTR 2 and 5**

Somatuline autogel (Lanreotide)

- 30,60,90mg prefilled syringe
- **Dose:** 30–60 mg deep subcutaneous every 4 weeks

Sandostatin LAR (octreotide)

- 10,20,30mg vials
- **Dose:** 10 mg intramuscularly every 4 weeks

Monitoring…

- Regular blood glucose monitoring
- **Liver function every** 3 months
- **Growth and thyroid function** at least 6-monthly
- **Abdominal ultrasound** every 6-12 months

Surgery

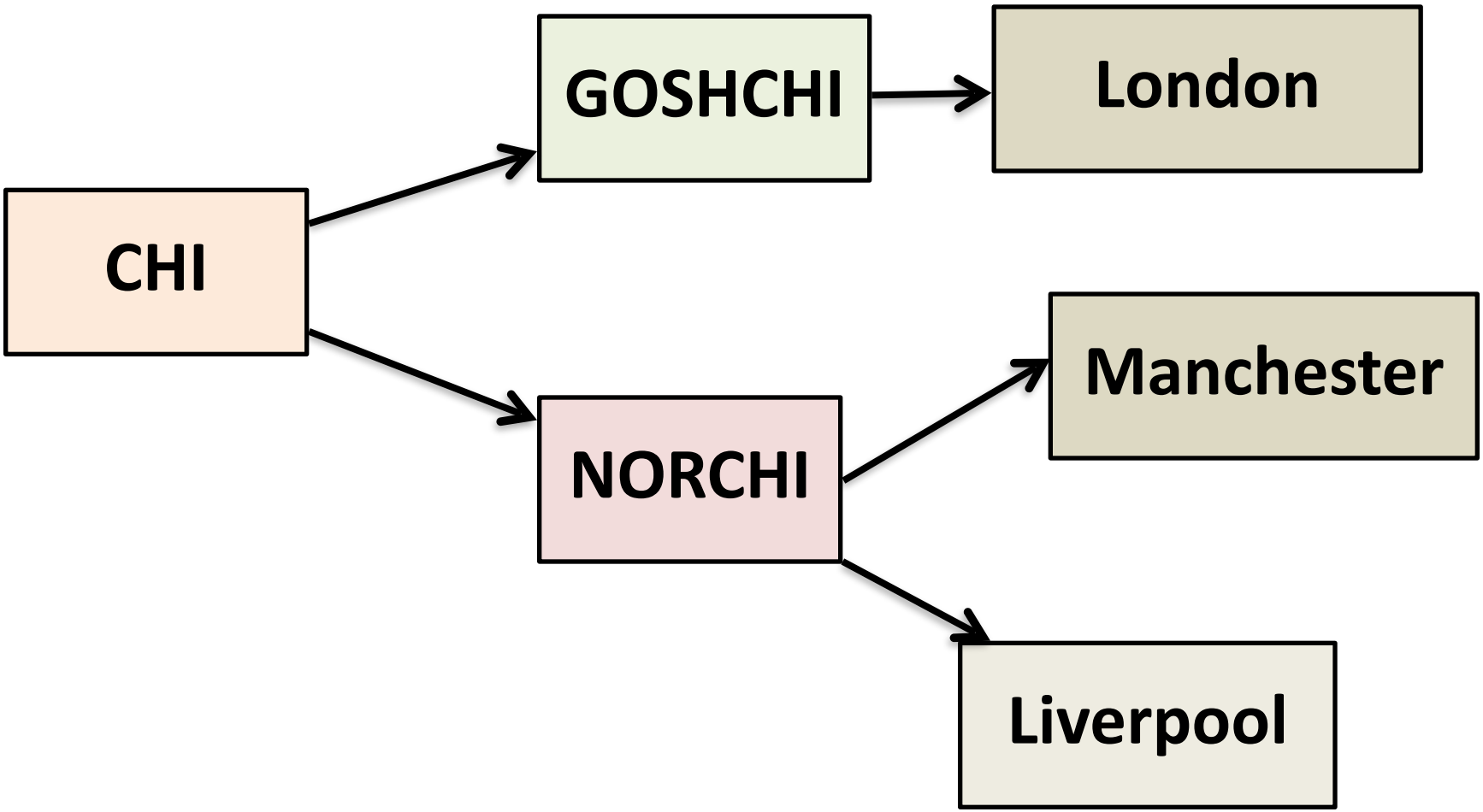
- Severe [medically unresponsive] diffuse CHI- 95% to 98% **pancreatectomy**

Surgery - Outcomes

- 105 children (58 diffuse)
- Diffuse - **59% still had hypoglycemia** requiring medical treatments (resolved by 5 years)
- **Hyperglycaemia** in 53% immediately after surgery & **100%** by 13 years of age

Glucose Metabolism in 105 Children and Adolescents After Pancreatectomy for Congenital Hyperinsulinism. Jacques Beltrand, Marylène Caquard, Jean-Baptiste Arnoux, Kathleen Laborde, Gilberto Velho, Virginie Verkarre, Jacques Rahier, Francis Brunelle, Claire Nihoul-Fékété, Jean-Marie Saudubray, Jean-Jacques Robert, and Pascale de Lonlay. Diabetes Care. 2012 Feb; 35(2): 198–203.

Quaternary MDT Centres for CHI (Nationally Commissioned)



Thank You