Hyperinsulinaemic Hypoglycaemia

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ISPAD Postgraduate Course in Varna, April 24-26, 2015
Aims

• Background to Hypoglycaemia

• Physiology of insulin secretion

• Biochemical and Genetic basis of Hyperinsulinaemic Hypoglycaemia (HH)

• Diagnostic and management cascade

• Review some novel forms and therapies for HH
Introduction

• Hypoglycaemia: Common

• Biochemical findings not a diagnosis

• Interpretation of blood glucose in context of clinical picture and intermediary metabolites
Physiology of Insulin Secretion
Insulin Secretion

GLUCOSE

- Amino Acids
- Fatty acids
- Neurotransmitters
- Gut hormones/GLP-1

Pancreatic $\beta$-cell

β-cells function as fuel sensors

Glucose is the prime regulator of insulin secretion

Glucose metabolism linked to insulin secretion

3.5-5.5 mmol/L
How is Glucose Metabolism Linked to β-Cell Insulin Secretion?
The Role of Pancreatic Beta-cell $K_{ATP}$ Channels
$K_{\text{ATP}}$ Channels and Insulin Secretion

SUR1

KIR6.2
$K_{ATP}$ Channels and Insulin Secretion

Glucose

$K_{ATP}$ Channel Pathway: “Trigger”

ATP:ADP
$K_{ATP}$ Channels and Insulin Secretion

Glucose

$K_{ATP}$ Channel Pathway: “Trigger”

ATP:ADP

$Ca^{2+}$

Insulin exocytosis
**K\textsubscript{ATP} Channels and Insulin Secretion**

Glucose

K\textsubscript{ATP} Channel Pathway: “Trigger”

ATP:ADP

Ca\textsuperscript{2+}

Signals from amplification pathway: “Amplification”

DAG, cAMP, PKs, etc

Insulin exocytosis

GPCR eg. ACh, GLP1, CCK, Lipids
Background to HH

- Inappropriate secretion of insulin in relation to the blood glucose concentration.

- Cause of recurrent and persistent hypoglycaemia in infancy and childhood.

- “Idiopathic hypoglycaemia of infancy," leucine sensitive hypoglycaemia, neonatal insulinoma, nesidioblastosis and Persistent Hyperinsulinaemic Hypoglycaemia of Infancy (PHHI).

- Major cause of hypoglycaemic brain injury
Hyperinsulinaemic Hypoglycaemia and Brain Injury: Importance of early diagnosis

MRI scan showing parieto-occipital brain damage
Background to HH

- **Transient**
  - IUGR
  - Perinatal asphyxia
  - Infant of diabetic mother
  - Syndromes (Beckwith-Weidemann)
  - “idiopathic”
Background to HH

- Fasting
- Post Prandial Hyperinsulinaemic Hypoglycaemia (PPHH)
- Protein induced
- Exercise induced HH
Syndromes and HH

• Many syndromes associated with HH
  - Beckwith-Wiedemann
  - Soto
  - Kabuki
  - Usher
  - Timothy
  - Costello
  - Trisomy 13
  - Mosaic Turner

• Most common: Beckwith-Weidemann
Beckwith-Weidemann Syndrome

- Macrosomia
- Exomphalas
- Macroglossia
- Ear creases
- Hypoglycaemia
- Organomegaly
- Predisposition to tumours
Persistent or Congenital Hyperinsulinism (CHI)
Background to CHI

• “Idiopathic hypoglycaemia of infancy", leucine sensitive hypoglycaemia, neonatal insulinoma, microadenomatosis, focal hyperplasia, nesidioblastosis and Persistent Hyperinsulinaemic Hypoglycaemia of Infancy (PHHI).
Background to CHI

- Incidence 1/35,000 in UK (1/10-15,000).

- Typically presents in neonatal period/infancy/childhood period.

- Hypoketotic, hypofattyacidaemic hyperinsulinaemic hypoglycaemia.

- Heterogeneous: clinical presentation, histology, molecular biology and genetics.
CHI in Macrosomic Babies
CHI in Non Macrosomic Babies
CHI in Preterm and IUGR Babies
So far mutations in 9 genes identified which lead to HH
## The Genetics of HH

<table>
<thead>
<tr>
<th>Gene Location</th>
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</table>
Causes of CHI: “Channelopathies”

- **ABCC8**
- **KCNJ11**

Autosomal recessive (usually medically unresponsive)

Autosomal dominant (medically responsive and unresponsive)
Glucose

$K_{ATP}$ Channels and Insulin Secretion

Glucose

$K_{ATP}$ Channel Pathway: “Trigger”

ATP:ADP

$Ca^{2+}$

$Ca^{2+}$

Insulin exocytosis

Signals from amplification pathway: “Amplification”

GPCR eg. ACh, GLP1, CCK, Lipids

DAG, cAMP, PKs, etc

ATP:ADP

Signals from amplification pathway: “Amplification”

GPCR eg. ACh, GLP1, CCK, Lipids

DAG, cAMP, PKs, etc
Defects in $K_{\text{ATP}}$ Channels Cause CHI

Channel Trafficking and Channel Regulation Defects

Glucose

$\text{ATP:ADP}$

Unregulated Insulin exocytosis


Defects in $K_{ATP}$ Channels Cause CHI

Channel Trafficking and Channel Regulation Defects

--


Typical Presentation

- Persistent Hypoglycaemia
- Not normally responsive to oral feeds
- Require concentrated Iv Dextrose to maintain normoglycemia
Management Cascade: Acute

• Stabilisation
  - Central venous access
  - Intravenous glucose/feeds
  - Fluid balance
  - Frequent blood glucose measurements
    \((BM > 3.5\text{mmol/L})\)
Diagnosis of HH
Biochemical Profile

- INCREASED GLUCOSE CLEARENCE RATE
- Plasma glucose 2.0mmol/L
- Insulin 7.5mU/L
- Cortisol 102nmol/L
- Glucagon 12
- GH 58mU/L
- Ammonia 36μmol/L (<40)
- Lactate 1.3mmol/L
- Serum NEFA 0.07mmol/L (Fatty acids)
- Serum β-HOB <0.05mmol/L (Ketone bodies)
- Carnitine/Acylcarnitine/Urine organic acids
Biochemical Studies in Patients With HH

CHI: Management Issues

- Patients have multiple problems
  - Fluid overload
  - Cardiac / respiratory failure
  - Problems related to central lines
  - Sepsis
  - Stress for parents
  - Feeding issues (loss of “orality”)
  - Gastro-oesophageal reflux
  - Feed associated hypoglycaemia (protein sensitivity)
Management Cascade

- Medical therapy
  - Diazoxide (+/- chlorothiazide)
  - Nifedipine
  - Glucagon
  - Octreotide (analogue of Somatostatin)
Diazoxide: Mechanism of Action

Glucose

Diazoxide binds to the KATP SUR1 subunit

Ca^{2+}

ATP:ADP

Insulin exocytosis
Diazoxide: Mechanism of Action

Diazoxide binds to the KATP SUR1 subunit

Glucose

ATP:ADP

Ca^{2+}

Insulin exocytosis
Nifedipine: Mechanism of Action

- Glucose
- ATP:ADP
- Nifedipine Blocks Calcium Channels
Octreotide: Mechanism of Action

Glucose

ATP:ADP

Octreotide has multiple actions

SSTS

Ca^{2+}

Ca^{2+}
Unresponsive to Medical Therapy—What’s the Next Step?
Management of Diffuse and Focal CHI

Diffuse

Focal
Histology of Focal CHI

Normal pancreas

Focal region
Histology of Diffuse CHI

Normal pancreas

Diffuse disease
Focal Form of CHI

- 40-50% of infants have focal.
- Distinct from insulinoma.
- 2-10mm in diameter.
- Current methods of imaging such as MRI and CT not able to localise.
Focal Form of CHI

- Localisation and removal of focal lesion is curative.
- Remaining pancreas “normal”
- Genetically distinct from diffuse disease.
Focal CHI

Can Be Found Anywhere In The Pancreas
Focal CHI

Can Be Found Anywhere In The Pancreas
Focal CHI

Can Be Found Anywhere In The Pancreas
Types Of Focal Lesions

Small Focal Lesion
Types Of Focal Lesions

A Focal Lesion with Tentacles
Types Of Focal Lesions

Giant Focal Lesion
Types Of Focal Lesions

Deep Lying Focal Lesions
Types Of Focal Lesions

Ectopic Focal Lesion
Management of Diffuse and Focal CHI

Near total pancreatectomy
High risk of diabetes mellitus

Limited resection offering “cure”
Focal Form of CHI

- Localisation and removal of focal lesion is curative.

- Remaining pancreas “normal”.

![Image of pancreas with focal lesion highlighted]
So How do we Distinguish Focal From Diffuse Forms of HH?
Use of 18F-DOPA-PET


How does 18F-DOPA-PET/CT work?
Dopamine Metabolism

Tyrosine → Tyrosine hydroxylase → 3,4 Dihydroxyphenylalanine (DOPA) → Dopa Decarboxylase → Dopamine → Catechol-O-methyltransferase (COMT) → 3-Methoxytyramine → Monoamine oxidase → 3,4 Dihydroxy-B-phenylacetaldehyde

Sequestered dopamine → Noradrenaline

Dopamine → Adrenaline
18F-DOPA-PET in CHI

- PET: functional uptake of 18F-DOPA
- Islets take up 18F-DOPA
- Intensity of uptake = metabolic activity
- Superimposed CT
18F-DOPA PET Images of Focal Lesions
Focal lesion at tip of pancreas, junction of spleen and left kidney (5.1mm).
Laparoscopic Surgery

Laparoscopic Surgery for Focal Lesions

- Enteral feeds after 24 hours
- Full feeds by day 5
- No wound problems
- Less need for analgesia
- So far no post op complications
Focal lesion in head of pancreas junction of portal vein and SMV (6.1mm)
Focal lesion in head of pancreas junction of portal vein and SMV (6.1mm)
18F-DOPA PET Images of Diffuse Lesions
18F-DOPA-PET: 3D imaging
Diffuse Disease: Near Total Pancreatectomy
Immediate Outcome of 45 Children with Medically Unresponsive Diffuse CHI Managed With Near-Total Pancreatectomy.

Cumulative Incidence of Hypoglycaemia (■), Hyperglycaemia (○), and insulin Therapy (●) in 58 Patients Pancreatectomized for Diffuse CHI

Protein Induced HH
# The Genetics of HH

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HADH/GDH Control Insulin Secretion in response to Protein and Fat Metabolism

Protein metabolism

Leucine

α-ketoglutarate + Ammonia

Protein metabolism → GDH

α-ketoglutarate + Ammonia → Glutamate

Glutamate → GTP

Fatty acid oxidation

HADH

3-oxidized fatty acyl-CoA → Dehydrogenase

Hydroxyacyl-CoA → β-Ketothiolase

β-Ketoacyl-CoA → Fatty acid oxidation

GTP

Leucine

Glutamate

α-ketoglutarate + Ammonia
Novel Genetic Mechanisms of HH
# The Genetics of HH

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HNF4Alpha and Hyperinsulinaemic Hypoglycaemia


The Role of HNF4A

- Orphan nuclear receptor
- Critical in regulating the expression of genes involved in regulating glucose induced insulin secretion
- Heterozygote mutations cause MODY1
The Role of HNF4A in Beta-cells

Kulkarni R et al Science VOL 303 27 FEBRUARY 2004
Family 1

- NM (17 INS)
- NM (c99.9 26 OHA)
- NM (c99.9)
- Continuing Diazoxide treatment at the age of 8 months

Family 2

- INS (20)
- Family 3

- NM (33)
- NM (c99.9)
- Diazoxide treated until 2 years 8 months

Family 3

- NM (31 OHA)
- NM (c99.9)
- Continuing Diazoxide treatment at the age of 18 months

Family Pedigrees
<table>
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<tr>
<th>Clinical Aspects</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Weight</strong></td>
<td>5900 grams</td>
<td>4200 grams</td>
<td>4005 grams</td>
</tr>
<tr>
<td><strong>Gestation</strong></td>
<td>39/40</td>
<td>37/40</td>
<td>36/40</td>
</tr>
<tr>
<td><strong>Age of presentation</strong></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 1</td>
</tr>
<tr>
<td><strong>Maximum Glucose Infusion Rate</strong></td>
<td>25 mg/kg/min</td>
<td>12.5 mg/kg/min</td>
<td>11 mg/kg/min</td>
</tr>
<tr>
<td><strong>Glucagon Infusion Required</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Diazoxide responsive (dose)</strong></td>
<td>Yes, 10 mg/kg/d</td>
<td>Yes, 10 mg/kg/d</td>
<td>Yes, on 6 mg/kg/d</td>
</tr>
<tr>
<td><strong>Family history of diabetes</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Attempted withdrawal of diazoxide</strong></td>
<td>Not successful at 7 months</td>
<td>Not successful at 18 months</td>
<td>Successful at 32 months</td>
</tr>
</tbody>
</table>

Kapoor RR et al. Persistent Hyperinsulinaemic Hypoglycaemia and Maturity Onset Diabetes of the Young (MODY) due to Heterozygous HNF4A Mutations. *Diabetes.* 2008 Feb 11
Novel Insights into The Role of HNF Transcription Factors


- Mutations in HNF1A (MODY3) can cause hyperinsulinism early in life and diabetes later
Hyperinsulinaemic Hypoglycaemia Due to Mutations in The HNF4Alpha gene

Mechanisms of Hyperinsulinaemic hypoglycaemia still unclear.

Hyperinsulinaemic hypoglycaemia and MODY1
Diffuse Disease: Challenges

• Unresponsive to - Diazoxide, Octreotide & Glucagon

• Severe forms - Pancreatectomy - an attempt to physically remove the mass of insulin secreting cells

• Even with 95 to 98% pancreatectomy – on-going hypoglycaemia

• Post op complications – diabetes mellitus, exocrine pancreatic insufficiency
Near Total Pancreatectomy
Diffuse Disease: Challenges

- Urgent need to develop new non-surgical treatment options which will reduce the risk of diabetes mellitus
So What is New in The Field of Diffuse Disease?
Diffuse Disease: Novel Treatments

- Long acting Octreotide
- KATP Channel Chaperones
- Insulin receptor antagonists
- GLP-1 receptor antagonists
- mTOR Inhibitors
Chaperone Agents
Glibenclamide Rescues Surface Expression of the A116P and V187D Mutant K$_{\text{ATP}}$ Channels.

Carbamazepine Corrects SUR1 Processing defects Caused by a Subset of Mutations Previously identified in CHI

Carbamazepine Restores Surface Expression of Trafficking-Impaired SUR1 Mutants.
In Vitro Recovery of ATP-Sensitive Potassium Channels in β-Cells From Patients With CHI

Powell PD et al. In-vitro recovery of ATP sensitive potassium channels in β-cell from patients with CHI. *Diabetes*, 2011;60; 1223-1228
Glucagon Like Peptide -1 (GLP-1) Receptor Antagonists
Summary of The Cellular Actions of GLP-1 That Lead to Stimulation of Insulin Secretion.

Holst J J Physiol Rev 2007;87:1409-1439
Exendin-(9–39)-Normalized Fasting Blood Glucose Levels in SUR-1−/− mice

<table>
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<tr>
<th>Condition</th>
<th>cAMP content</th>
<th>Insulin secretion</th>
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<tbody>
<tr>
<td>Base line (n = 3)</td>
<td>40 ± 4 pmol/100 islets</td>
<td>221 ± 22 ng/100 islets/30 min</td>
</tr>
<tr>
<td>100 nm exendin-(9-39) (n = 3)</td>
<td>21 ± 2 pmol/100 islets</td>
<td>126 ± 17 ng/100 islets/30 min</td>
</tr>
<tr>
<td>4 mm AAM (n = 8)</td>
<td>73 ± 13 pmol/100 islets</td>
<td>360 ± 32 ng/100 islets/30 min</td>
</tr>
<tr>
<td>100 nm exendin-(9-39)/4 mm AAM (n = 4)</td>
<td>24 ± 5 pmol/100 islets</td>
<td>190 ± 35 ng/100 islets/30 min</td>
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AAM: Amino Acid Mixture

GLP-1 Receptor Antagonist Exendin-(9-39) Elevates Fasting Blood Glucose Levels in CHI due to Inactivating Mutations in the ATP-Sensitive K+ Channel

**TABLE 1**

<table>
<thead>
<tr>
<th>Subject (years)</th>
<th>Sex</th>
<th>Mutation (ABCC8)</th>
<th>Pancreatectomy</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>F</td>
<td>delF1388/3992-9 G&gt;A</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>M</td>
<td>delS1387*</td>
</tr>
<tr>
<td>3</td>
<td>35</td>
<td>M</td>
<td>S408P*</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>F</td>
<td>3992-9 G&gt;A/3992-9 G&gt;A</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>F</td>
<td>3992-9 G&gt;A/3992-9 G&gt;A</td>
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<tr>
<td>6</td>
<td>18</td>
<td>M</td>
<td>delS1387*</td>
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<tr>
<td>7</td>
<td>16</td>
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</tr>
<tr>
<td>8</td>
<td>47</td>
<td>F</td>
<td>R1353H*</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>R521Q*</td>
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F, female; M, male. *Dominant mutation.

Calabria AC et al. *Diabetes* 2012, 61;2585-2590.
GLP-1 Receptor Antagonist Exendin-(9-39) Elevates Fasting Blood Glucose Levels in CHI due to Inactivating Mutations in the ATP-Sensitive K+ Channel

Calabria AC et al. *Diabetes* 2012, 61;2585-2590.
Proposed Mechanism of Action of Exendin-(9–39) in SUR-1--/-- Islets

Insulin Receptor Blocking Antibodies
XMetD Reverses Insulin-Induced Hypoglycemia in Mice

Normal mice given insulin implants and fasting glucose levels measured after no treatment or following treatment with either 10 mg/kg XMetD or control IgG.

Corbin JA et al Inhibition of insulin receptor function by a human, allostERIC monoclonal antibody: a potential new approach for the treatment of hyperinsulinemic hypoglycemia. MAbs. 2014 Jan-Feb;6(1):262-72
Novel Octreotide Formulations
Long Acting Octreotide Formulations


Le Quan Sang KH et al. Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur J Endocrinol*. 2012 Feb;166(2):333-9. 10 paediatric patients with HI unresponsive to diazoxide and treated with s.c. octreotide were included.
Inhibitors of the mTOR Pathway
mTOR Pathway

Growth Factors: IGF-1, VEGF, ErbB, Glucose, FA, AA

PTEN

O2, energy, nutrients

TSC2/TSC1

Ras/Raf pathway

PI3-K

PTEN

Akt/PKB

Ras/Raf
Abl
ER

mTOR

S6K1

S6

Protein Synthesis

Cell Growth and Proliferation

Angiogenesis

4E-BP1

eIF-4E

β-cells

Insulin Secretion

Metabolism

Reactive O2 Species

Stress Resistance

Insulin Resistance

Periphery

Bourcier ME. et al. J Clin Endocrinol Metab 2009;94:3157-3162
β-cell Hyperplasia

- Enhanced β-cell proliferation noted in diffuse HH when compared to age-matched controls*

- We compared the gene expression pattern in pancreatic tissues of diffuse HH with normal

- Affymetrix Human GeneChip® 1.0 ST Array

What Have We Learned!

• Growth factors likely involved in β-cell proliferation in diffuse HH

• Activated mTOR pathway – key mechanism

• Transdifferentiation of acinar cells of exocrine pancreas
mTOR Inhibitors

- Sirolimus (Rapamycin) - used successfully in an elderly patient with pancreatic insulin secreting tumour

- Four adult patients with metastatic insulinoma showed significant glycaemic response to treatment with everolimus

Four consecutive infants with HH unresponsive to maximal doses of diazoxide (20mg/kg/day) and octreotide (35mcg/kg/day)

Sirolimus - commenced at 0.5mg/m2/day & gradually increased aiming for a trough serum level of 5-15ng/ml
Sirolimus Therapy in Infants with Severe Hyperinsulinemic Hypoglycemia


SUMMARY

Hyperinsulinemic hypoglycemia is the most common cause of severe, persistent neonatal hypoglycemia. The treatment of hyperinsulinemic hypoglycemia that is unresponsive to diazoxide is subtotal pancreatectomy. We examined the effectiveness of the mammalian target of rapamycin (mTOR) inhibitor sirolimus in four infants with severe hyperinsulinemic hypoglycemia that had been unresponsive to maximal doses of diazoxide (20 mg per kilogram of body weight per day) and octreotide (35 μg per kilogram per day). All the patients had a clear glycemic response to sirolimus, although one patient required a small dose of octreotide to maintain normoglycemia. There were no major adverse events during 1 year of follow-up.

Hyperinsulinemic Hypoglycemia, a Major Cause of Severe Hypoglycemia during the neonatal period, is characterized by inappropriate insulin secretion from pancreatic beta cells in the presence of low blood glucose levels.¹ The condition may result from defects in key genes involved in the regulation of insulin secretion from beta cells, including ABCS8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A, and UCP2.² ³ Two major histologic subtypes have been described: diffuse and focal.⁴

Mutations in ABCS8 and KCNJ11 are associated with severe hyperinsulinemic hypoglycemia that is unresponsive to medical treatment with diazoxide and octreotide.⁵ The only treatment option currently available for patients with medically unresponsive forms of diffuse hyperinsulinemic hypoglycemia is a subtotal pancreatectomy, in which 95 to 98% of insulin-secreting cells are physically removed to alleviate the severe hypoglycemia. However, some patients who have undergone surgery continue to have recurrent hyperinsulinemic hypoglycemia, whereas diabetes mellitus and exocrine pancreatic insufficiency develop in others. In a recent study of 105 affected children who underwent pancreatectomy, 59% had persistent hyperinsulinemic hypoglycemia up to 5 years after surgery, and diabetes mellitus had developed in all the children by the time they reached early adolescence.⁶ Hence, there is a need for a medical therapy that can be used as an alternative to subtotal pancreatectomy.

A possible mechanism of hyperinsulinism and beta-cell hyperplasia in diffuse hyperinsulinemic hypoglycemia involves the constitutive activation of the mTOR pathway.⁷ The serine–threonine protein kinase mTOR has been implicated in the cellular response to nutrients and growth factor signaling.⁸ The mTOR pathway is
How Might Sirolimus be Working?

- Immediate effect – reduced insulin secretion
- Reduced mitochondrial ATP production
- Suppresses β-cell proliferation by inhibition of mTORC1 pathway
- Induces peripheral insulin resistance by impairing AKT activation and insulin signalling
Key Findings

- Preliminary data in small group of infants – Sirolimus can be safe and effective in the severe forms of HH

- Can be considered as an alternative to near total pancreatectomy in select groups of patients

- Larger studies - long term adverse effects, efficacy & molecular mechanisms
Conclusions

• HH is due to unregulated insulin secretion and is cause of severe hypoglycaemia.

• Early recognition and prompt treatment are vital in preventing hypoglycaemic brain damage.

• Differentiation of focal and diffuse disease

• New treatments for diffuse disease on the horizon
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