Hyperinsulinaemic hypoglycaemia: genetic mechanisms, diagnosis and management

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Abstract Hyperinsulinaemic hypoglycaemia (HH) is due to the unregulated secretion of insulin from pancreatic β-cells. A rapid diagnosis and appropriate management of these patients is essential to prevent the potentially associated complications like epilepsy, cerebral palsy and neurological impairment. The molecular basis of HH involves defects in key genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2) which regulate insulin secretion. The most severe forms of HH are due to loss of function mutations in ABCC8/KCNJ11 which encode the SUR1 and KIR6.2 components respectively of the pancreatic β-cell K<sub>ATP</sub> channel. At a histological level there are two major forms (diffuse and focal) each with a different genetic aetiology. The diffuse form is inherited in an autosomal recessive (or dominant) manner whereas the focal form is sporadic in inheritance and is localised to a small region of the pancreas. The focal form can now be accurately localised pre-operatively using a specialised positron emission tomography scan with the isotope Fluorine-18L-3, 4-dihydroxyphenyalanine (18F-DOPA-PET). Focal lesionectomy can provide cure from the hypoglycaemia. However the diffuse form is managed medically or by near total pancreatectomy (with high risk of diabetes mellitus). Recent advances in molecular genetics, imaging with 18F-DOPA-PET/CT and novel surgical techniques have changed the clinical approach to patients with HH.

Introduction

Hyperinsulinaemic hypoglycaemia (HH) is a major cause of persistent and recurrent hypoglycaemia in the neonatal and infancy periods. It is characterised by inappropriate and unregulated secretion of insulin from pancreatic β-cells in relation to the blood glucose concentration. A rapid diagnosis and appropriate management of these patients is essential to prevent the potentially associated complications like epilepsy, cerebral palsy and neurological impairment (Aynsley-Green et al. 2000). Patients with HH have increased risk of brain injury secondary to the metabolic actions of insulin, which acts by driving glucose into the insulin sensitive tissues (skeletal muscle and adipose tissue) and by inhibiting glucose production by glycolysis and gluconeogenesis (Hussain et al. 2007). It also inhibits fatty acid release and ketone body synthesis; hence the brain is deprived of both its primary and secondary energy sources (glucose & ketone bodies).

HH can be congenital (congenital hyperinsulinism, CHI) or secondary to certain risk factors like birth asphyxia, intrauterine growth retardation (Collins and Leonard 1984) and maternal diabetes mellitus or associated with developmental syndromes like Beckwith-Wiedemann syndrome (Muribns and Batch 2001). Some rare metabolic conditions like...
congenital disorders of glycosylation (CDG syndromes) are also associated with HH (Bohles et al. 2001).

CHI is a heterogeneous condition in terms of clinical presentation, histological subgroups and underlying molecular biology. The incidence of CHI can vary from 1 in 35,000–40,000 in the general population (Bruining 1990) to 1 in 2500 in some communities with high rates of consanguinity (Mathew et al. 1988). Mutations have been described in eight different genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2) that are involved in regulating insulin secretion from β-cells (for review see James et al. 2009). Two major histological subtypes of CHI (diffuse and focal) have been described (Rahier et al. 2000). The diffuse form is inherited in an autosomal recessive (or dominant) manner whereas the focal form is sporadic in inheritance. A specialised positron emission tomography scan using Fluroine-18L-3, 4-dihydroxyphenyalanine (18F-DOPA-PET) as the isotope is used to localise the focal lesions within the pancreas (Otonkoski et al. 2006). The focal type of HH can be completely cured by focal lesionectomy whereas the diffuse form is managed medically or by near total pancreatectomy. This review article provides an overview of HH, its clinical presentation, molecular basis, the diagnostic pathway and the management of different types of HH with special emphasis on CHI.

Pancreatic β-cell physiology, glucose metabolism and insulin secretion

The pancreatic β-cell ATP–sensitive K⁺ channel (K\textsubscript{ATP} channel) plays a crucial role in glucose homeostasis by linking glucose metabolism to electrical excitability and insulin secretion (Ashcroft et al. 1984). The β-cell K\textsubscript{ATP} channel is a hetero-octameric complex composed of two types of subunits: four inward-rectifying potassium channel pore-forming (Kir6.2) subunits and four high-affinity sulfonylurea receptor 1 (SUR 1) subunits (Inagaki et al. 1995). The Kir6.2 forms the pore of the channel and the SUR1 (an ATP binding cassette transporter) acts as a regulatory subunit. K\textsubscript{ATP} channels are regulated by adenine nucleotides to convert changes in cellular metabolic levels into membrane excitability (Cook and Hales 1984). The Kir6.2 subunit determines the biophysical properties of the channel complex including K⁺ selectivity, rectification, and inhibition by ATP and activation by acyl-CoAs (Tucker et al. 1998). The sulfonylurea receptors endow K\textsubscript{ATP} channels with sensitivity to the stimulatory actions of Mg-nucleotides and K\textsubscript{ATP} channel openers like diazoxide and the inhibitory effects of sulfonylureas (Aguilar-Bryan et al. 1995).

The concentration of blood glucose directly determines the rate of glucose oxidation in β-cells and subsequently controls insulin secretion. Glucose metabolism raises the intracytosolic ATP/ADP ratio which inhibits the plasma membrane sulfonylurea receptor 1(SUR 1). This results in the closure of the K\textsubscript{ATP} channel which in turn leads to cell membrane depolarisation and Ca\textsuperscript{2+} influx via voltage gated calcium channels. The increase in the cellular concentration of calcium triggers the release of insulin from storage granules. When glucose levels are low, K\textsubscript{ATP} channels are open and potassium diffusing via these channels maintains the resting membrane potential at a hyperpolarized level.

Aetiology of HH

Transient HH

Transient HH is poorly defined term that generally refers to the group of patients in whom HH resolves spontaneously within few days to about a week. The transient form of HH is associated with maternal diabetes mellitus (gestational or insulin dependent), intra-uterine growth retardation, perinatal asphyxia, erythroblastosis fetalis, after the maternal administration of drugs such as sulphonylureas, and after intravenous maternal glucose infusions during labour. The transient form may also be “idiopathic” with no risk factor for hyperinsulinism (Yap et al. 2004). Some patients with intra-uterine growth retardation and asphyxia have a protracted form of HH which resolves over several months and may require treatment with diazoxide (Fafoula et al. 2006). The mechanism/s causing transient HH in these conditions is not clear.

Congenital hyperinsulinism (see Fig. 1)

(a) Pancreatic β-cell K\textsubscript{ATP} channel defects

The Kir6.2 and SUR1 subunits are encoded by the genes KCNJ11 and ABCC8 (both genes localised to chromosome 11p15.1), respectively, the mutations in which result in CHI. Recessive inactivating (loss of function) mutations in ABCC8 and KCNJ11 are the most common causes of CHI (Thomas et al. 1995; 1996). The inactivating mutations in ABCC8/KCNJ11 reduce or completely abolish the activity of the K\textsubscript{ATP} channel, leading to unregulated insulin secretion despite severe hypoglycaemia (Kane et al. 2000). Germline mutations in either ABCC8 or KCNJ11 are identified in approximately 50% of CHI patients (Flanagan et al. 2009).

To date 150 homozygous, compound heterozygous and heterozygous inactivating mutations in ABCC8 have been reported (Flanagan et al. 2009). Around 24 KCNJ11 mutations have been found in CHI, all of which either reduce or abolish K\textsubscript{ATP} channel activity in the surface membrane (Flanagan et al. 2009). The recessive inactivating mutations in ABCC8 and KCNJ11 usually cause severe CHI which is unresponsive to medical treatment with diazoxide. The molecular basis of recessive inactivating ABCC8 and KCNJ11...
mutations involves defects in $K_{ATP}$ channel biogenesis and turnover (Crane and Aguilar-Bryan 2004), in channel trafficking from the ER and Golgi apparatus (Cartier et al. 2001; Yan et al. 2007) to the plasma membrane and alterations of channels in response to both nucleotide regulation and open state frequency (Lin et al. 2006). Dominant inactivating mutations in $ABCC8$ and $KCNJ11$ usually cause CHI with a milder phenotype (Huopio et al. 2000; Pinney et al. 2008), although medically unresponsive forms have been reported recently (Flanagan et al. 2011a, b).

(b) Hyperinsulinism-hyperammonaemia syndrome (HI/HA)

Hyperinsulinism-hyperammonaemia syndrome (HI/HA) is associated with dominant missense mutations of the mitochondrial matrix enzyme, glutamate dehydrogenase (GDH) (Stanley et al. 1998). These mutations lead to a gain of enzyme function by reducing its sensitivity to allosteric inhibition by the high-energy phosphates such as GTP and ATP and allowing activation by the amino acid leucine (Stanley et al. 1998). GDH catalyses the reversible oxidative deamination of glutamate to alpha-ketoglutarate and ammonia using NAD or NADP as co-factors. The increased GDH activity leads to inappropriate insulin secretion in pancreatic $\beta$-cells, as well as to excessive ammonia production and reduced urea synthesis in the liver. Recent animal studies have suggested the role of renal ammoniagenesis due to activation of GDH as a source of hyperammonemia in these patients (Treberg et al. 2010).

The phenotype is characterised by recurrent postprandial hypoglycaemia following protein-rich meals as well as fasting hypoglycaemia accompanied by asymptomatic 2 to 5 fold elevations of plasma ammonia (Hsu et al. 2001). Urinary alpha-ketoglutarate excretion is raised in HI/HA patients (Meissner et al. 2004).

Though hyperammonaemia has remained the most consistent feature of HI/HA, there are a rare group of patients who demonstrate leucine hypersensitivity but have a persistently normal serum ammonia level (Kapoor et al. 2009a, b, c). These patients may be mosaic for GDH enzyme activity (with normal GDH activity in the liver but elevated activity in the pancreas) however this remains to be proven. The phenotype is reported to be milder in contrast to other forms of CHI, thus escaping recognition for the first few months of life (Kapoor et al. 2009a, b, c).

In contrast to hyperammonaemia patients due to urea cycle disorders, patients with HI/HA syndrome do not experience lethargy, headaches, or manifest CNS symptoms that might be expected for their degree of hyperammonaemia, and are resistant to ammonia scavenging agents or protein restriction. On the other hand, neurological complications such as epilepsy and learning disabilities develop more frequently (Bahi-Buisson et al. 2008). Routine measurement of
plasma ammonia concentrations in all patients with hypoglycaemia is an essential screening test for the disorder.

(c) HADH and hyperinsulinism

A mutation in the mitochondrial HADH gene (encoding the enzyme L-3-hydroxyacyl-Coenzyme A dehydrogenase (HADH), which is involved in the penultimate step of the β-oxidation pathway) is a rare cause of CHI (Clayton et al. 2001). The enzyme catalyses the conversion of L3-hydroxyacyl CoAs of variable chain length to their corresponding 3-ketoacyl CoAs and exercises highest activity to 3-hydroxybutyryl-CoA. HADH gene has been mapped to chromosome 4q22-26 (Vredendaal et al. 1996) and is expressed in most tissues, although the enzyme activity is high in the pancreas, particularly in the islets of Langerhans (Hardy et al. 2007a, b). HADH expression is regulated by transcription factors such as Foxa2, which are essential for β-cell differentiation and mice which have Foxa2 knocked out, showed a 3-fold down regulation of HADH mRNA and severe HH (Sund et al. 2001).

HADH gene mutations can lead either to severe neonatal HH or to mild late onset HH (Molven et al. 2004; Martins et al. 2011). All patients reported so far have responded to diazoxide and some had abnormal acylcarnitine metabolites (raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate levels). Protein sensitivity has been demonstrated in patients with HADH mutations (Kapoor et al. 2009a, b, c) and this has been confirmed in the HADH knockout mouse (Li et al. 2010). However the precise mechanism of dysregulated insulin secretion in patients with a HADH deficiency is not understood but might involve an interaction between GDH and HADH (Li et al. 2010). Genetic analysis for HADH gene is recommended in patients with diazoxide responsive HH from consanguineous families, who are negative for mutations in the KATP channels (Flanagan et al. 2011a, b).

(d) HNF4A and hyperinsulinism

HNF4A gene encodes for the transcription factor HNF-4α (Hepatocyte Nuclear Factor 4alpha), which belongs to the nuclear hormone receptor superfamily and has been shown to control the expression of genes involved in glucose stimulated insulin secretion (Gupta et al. 2005). Heterozygous mutations in the HNF4A gene cause maturity-onset diabetes of the young type 1 (MODY1), which is characterised by progressive β-cell dysfunction and failure of glucose induced insulin secretion (Yamagata et al. 1996). Recently heterozygous mutations in the HNF4A gene were also reported to result in transient (Pearson et al. 2007) or persistent HH (Kapoor et al. 2008).

The phenotype of these patients is characterised by macrosomia and neonatal HH (Fajans and Bell 2007; Pingul et al. 2011). The severity of HH in these patients varies from diet-controlled neonatal hypoglycaemia to persistent HH requiring diazoxide treatment. In a recent series of 11 patients with HNF4A mutations, the HH was noted to range from 3 months to 8 years with ongoing need for diazoxide therapy (Flanagan et al. 2010). Interestingly, only few of the parents of children in this series had diabetes, suggesting that the absence of a history of diabetes in the parents should not preclude sequencing of the HNF4A gene. HNF4A mutation has been noted to have variable penetrance with only a minority of HNF4A mutation carriers developing HH. The precise mechanism by which HNF4A mutations cause HH is not clear but might involve a reduction in expression of the potassium channel subunit Kir6.2 (Gupta et al. 2005) or reduction in the levels of PPARα (Gremlich et al. 2005).

PPARα is a transcription factor that is known to control the expression of genes encoding enzymes in the beta oxidation pathway of fatty acids. Low levels of PPARα are reported in HNF-4α deficient beta cells (Gupta et al. 2005). It can be postulated that HNF-4α deficiency causes lower levels of PPARα and a decrease in beta-oxidation of fatty acids resulting in the accumulation of lipids (such as malonyl-CoA) in the cytoplasm. Increased malonyl-CoA is thought to inhibit the enzyme carnitine-palmitoyltransferase1 thereby increasing cytosolic long-chain acyl-CoA levels, which signals insulin release (Prentki et al. 2002). In support of this hypothesis PPARα null mice develop fasting HH suggesting that PPARα is important for regulated insulin secretion during fasting (Gremlich et al. 2005).

(e) Exercise-induced hyperinsulinism (SLC16A1)

Exercise-induced hyperinsulinism (EIHI) is a dominantly inherited hypoglycaemic disorder characterised by inappropriate insulin secretion during anaerobic exercise or on pyruvate load (Meissner et al. 2001; Otonkoski et al. 2003; Meissner et al. 2005). To date, 13 patients have been reported. 12 from two Finnish pedigrees and one unrelated patient (Otonkoski et al. 2007). Affected patients become hypoglycaemic typically 30 to 45 minutes after a period of intensive anaerobic exercise (Meissner et al. 2005).

The transport of lactate and pyruvate are mediated by monocarboxylate transporter 1 (MCT1) which is encoded by the SLC16A1 (solute carrier family 16, member 1) gene. Under normal physiological conditions lactate and pyruvate concentrations are low in β-cells and they do not stimulate insulin secretion (Zhao et al. 2001). However promoter-activating mutations in SLC16A1 induce the expression of MCT1 in β-cells (where this gene is not usually transcribed), permitting pyruvate uptake and pyruvate-stimulated insulin release despite ensuing hypoglycaemia (Otonkoski et al. 2007). This novel disease mechanism results from the failure of cell-specific transcriptional silencing of a gene (SLC16A1) that is highly expressed in other tissues. During strenuous anaerobic exercise there is accumulation of lactate and
pyruvate which then act as insulin secretagogues. Treatment is not usually necessary as hypoglycaemic episodes may be prevented by avoiding strenuous exercise.

(f) Glucokinase induced hyperinsulinism

Glucokinase is a key glycolytic enzyme that plays a pivotal role as a glucose sensor in the pancreatic β-cell and appears to have a similar role in entero-endocrine cells, hepatocytes, and hypothalamic neurons (Matschinsky 2002). In β-cells, glucokinase a rate-limiting enzyme for glucose metabolism governs glucose-stimulated insulin secretion. Heterozygous activating mutations of glucokinase lead to CHI (Glaser et al. 1998). These glucokinase mutations result in increased affinity of the enzyme for glucose, resulting in an increase in the ATP: ADP ratio in the pancreatic β-cell, closure of K$_{ATP}$ channel, and inappropriate insulin secretion. The activating glucokinase mutations are inherited in an autosomal dominant manner with the severity of symptoms varying markedly within and between families (Wabitsch et al. 2007). The age of presentation of glucokinase induced hyperinsulinism can range widely from infancy to adulthood (Sayed et al. 2009). Affected children have fasting hypoglycaemia and may manifest variable responsiveness to medical treatment. Some appear to respond well to pharmacologic intervention with diazoxide, whilst others require more intensive medical management including octreotide and even surgery (Cuesta-Munoz et al. 2004).

(g) Mutations in the UCP2 gene and HH

The mitochondrial uncoupling protein 2 (UCP2) is a negative regulator of insulin secretion, by decreasing ATP/ADP ratio in β-cells and or modulating reactive oxygen species production (Chan et al. 2001). A few patients have been described with mild HI due to loss of function mutations in the UCP2 gene (González-Barroso et al. 2008).

**Metabolic conditions associated with HH**

(a) Congenital disorders of glycosylation (CDG)

Congenital disorders of glycosylation (CDG) are a rapidly evolving family of inherited multisystem disorders resulting from defects in the synthesis of the glycan moiety of glycoconjugates (mainly glycoproteins or glycolipids) or in the attachment of glycans to macromolecules (Jaeken 2003). Glycoconjugates play various crucial metabolic roles including cell-cell interaction, intracellular trafficking, proper protein folding, protease resistance, host defence and antigenicity. CDG type Ia is the most common and is caused by mutations in the phosphomannomutase 2 gene (PMM2) gene. The clinical spectrum of CDG type Ia has expanded since its initial description to now include rare features such as hyperinsulinaemic hypoglycaemia, congenital nephrotic syndrome and obstructive cardiomyopathy (Böhles et al. 2001). A milder disease with single organ involvement, presenting as isolated hyperinsulinaemic hypoglycaemia has been reported in a female patient (Shanti et al. 2009).

Hyperinsulinaemic hypoglycaemia as a leading symptom has been described predominantly in CDG type Ib (phosphomannose-isomerase deficiency) (Böhles et al. 2001). The phenotype is characterised by protein-losing enteropathy, congenital hepatic fibrosis, and coagulopathy without overt neurologic manifestations that are commonly seen in other CDGs. Early diagnosis is essential, because patients can be successfully treated with oral mannose. HH has also been described in patients with CDG Id (Sun et al. 2005).

The precise mechanism for insulin dysregulation is unknown, but the rapid resolution of HH in CDG type Ib patients with oral mannose supplementation suggests a role of glycosylation in maintenance of normoglycaemia, perhaps at the level of the sulfonylurea receptor. Abnormal glycosylation of SUR1/Kir6.2 however, may not be the primary cause of hypoglycaemia in these patients as observed by the response of most CDG patients with HH to diazoxide. CDGs should be considered in patients with HH of undiagnosed aetiology.

(b) Tyrosinaemia type I and HH

Tyrosinaemia type I results from deficiency of the enzyme fumarylacetoacetate hydrolase (FAH), encoded by FAH. The typical manifestations lead to severe liver and kidney disease. Recently three patients with Tyrosinaemia type I and liver impairment were reported to have HH (Baumann et al. 2005). Hypoglycaemia persisted despite dietary treatment and all three patients were successfully treated with diazoxide and chlorothiazide with treatment gradually being withdrawn after 9, 13 and 34 months, respectively. The mechanism of HH in patients with Tyrosinaemia type I is not known but may be related to the toxic metabolites that accumulate in this condition. (Table 1)

**Postprandial forms of HH**

Postprandial hyperinsulinaemic hypoglycaemia (PPHH) refers to the development of hypoglycaemia within a few hours of meal ingestion. It is associated with inappropriate insulin secretion in response to the meal. The most common cause is due to the “dumping” syndrome in infants who have undergone gastro-oesophageal surgery (Bufler et al. 2001). It has also been observed in patients who have undergone gastric bypass surgery for morbid obesity (Foster-Schubert 2011). It has been noted that children with PPHH after Nissen fundoplication have abnormally exaggerated secretion of Glucagon Like Peptide-1 (GLP-1) which may contribute to the exaggerated insulin surge and resultant hypoglycaemia (Palladino et al. 2008a, b).
PPHH is also observed in the insulin autoimmune syndrome which is characterised by the presence of insulin-binding autoantibodies in subjects who have not been previously exposed to exogenous insulin (Hirata 1973).

A syndrome of autosomal dominant PPHH with onset in adolescence to adulthood and linked to a mutation (Arg1174Gln) in the insulin receptor kinase gene has been reported (Højlund et al. 2004). Impaired insulin clearance and insulin resistance due to mutations in insulin receptor have been hypothesised to affect insulin action differently in various tissues leading to hypoglycaemia.

In adults, a syndrome of “non-insulinoma pancreatogenous” PPHH has been recognised (Service et al. 1999). These patients demonstrate neuroglycopenic episodes from hypoglycaemia within 4 h of meal ingestion and have negative 72-h fasts. The exact mechanism of hypoglycaemia is not clear (Table 2).

**Syndromes associated with HH**

Most CHI patients present with isolated hypoglycaemia. However, a large number of developmental syndromes may present in the newborn period with HH (Table 3). The most common syndrome associated with HH is Beckwith Wiedemann syndrome (BWS) (Munns and Batch 2001). This syndrome is characterised by prenatal and/or postnatal overgrowth, macroglossia, anterior abdominal wall defects, organomegaly, hemihypertrophy, ear lobe creases, helical pits, and renal tract abnormalities. HH is observed in about 50% of patients with BWS and in the vast majority of patients with

### Table 1 Diagnostic criteria for patients with HH

| Glucose infusion rate >8 mg/kg/min |
|-----------------------------------|
| Laboratory blood glucose <3 mmol/l with: |
| Detectable serum insulin/C-peptide |
| Suppressed/low serum ketone bodies |
| Suppressed/low serum fatty acids |
| Serum ammonia level may be raised (HI/HA syndrome) |
| Raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate (HADH deficiency) |
| Supportive evidence (when diagnosis is in doubt or difficult): |
| Positive glycaemic (>1.5 mmol/L) response to intramuscular/ intravenous glucagon |
| Positive glycaemic response to a subcutaneous/ intravenous dose of octreotide |
| Low serum levels of IGFBP1 [insulin negatively regulates the expression of IGFBP1] |
| Suppressed branch chain (leucine, isoleucine and valine) amino acids |
| Provocation tests (leucine loading or exercise testing) may be needed in some patients |

### Table 2 Summary of the drugs used in the management of patients with HH

| Medication | Route of administration | Dose | Mechanism of action | Side effects |
|------------|-------------------------|------|---------------------|-------------|
| Diazoxide  | Oral                    | 5-20 mg/kg/day divided into 3 doses | Opens a fully intact and functional $K_{ATP}$ channel | Common: fluid retention, hypertrichosis, Uncommon: hyperuricaemia, eosinophilia, leukopaenia, rarely hypotension |
| Chlorothiazide | Oral                  | 7-10 mg/kg/day divided into 2 doses | Used in conjunction with diazoxide for diuretic effect | Common: hyponatraemia, hypokalaemia |
| Glucagon   | SC/IV infusion for maintenance use IM/IV injection for emergency use | 1-20 μg/kg/hour maintenance use 0.5-1 mg in emergency | Increases blood glucose levels by stimulating glycogenolysis and gluconeogenesis | Nausea, vomiting, paradoxical insulin secretion in high doses Skin rashes |
| Octreotide | SC/IV continuous infusion 6-8 hourly SC injections | 5-35 μg/kg/day | Multiple actions: 1) inhibition of insulin exocytosis 2) Stabilisation of $K_{ATP}$ channels 3)? Inhibiting entry of calcium into $\beta$-cells | Common: cholelithiasis (not dose related), tolerance effect Uncommon: Suppression of growth hormone, thyroid stimulating hormone, glucagon, diarrhoea, steatorrhoea, abdominal distension (necrotising colitis), growth suppression. |
Table 3 Summary of the syndromes associated with hyperinsulinaemic hypoglycaemia

| Developmental syndromes                              | References                                      |
|------------------------------------------------------|-------------------------------------------------|
| Pre and post-natal overgrowth syndromes              |                                                 |
| i. Beckwith-Wiedemann syndrome                       | Moncrieff et al. 1977 and Hussain et al. 2005   |
| ii. Sotos syndrome                                   | Baujat et al. 2004                              |
| iii. Simpson Golabi Behmel syndrome                  | Terespolsky et al. 1995                         |
| Chromosomal abnormality syndromes                    |                                                 |
| i. Trisomy 13 (Patau syndrome)                       | Bellaton et al. 2002                            |
| ii. Mosaic Turner syndrome                           | Alkhayyat et al. 2006                           |
| Postnatal growth failure syndromes                  |                                                 |
| i. Kabuki syndrome                                   | White et al. 2004                               |
| ii. Costello syndrome                                | Dickson et al. 2004                             |
| Contiguous gene deletion affecting the ABCC8 gene    |                                                 |
| i. Usher syndrome                                    | Itin et al. 2000                                |
| Syndromes leading to abnormalities in calcium homeostasis |                                             |
| i. Timothy syndrome                                  | Splawski et al. 2004                            |
| ii. Congenital disorder of Glycosylation syndromes   |                                                 |
| i. Congenital disorder of Glycosylation 1a           | Böhles et al. 2001                              |
| ii. Congenital disorder of Glycosylation 1b          | De Lonlay et al. 1999                           |
| iii. Congenital disorder of Glycosylation 1d         | Sun et al. 2005                                 |
| Others                                               |                                                 |
| i. Congenital central hypoventilation syndrome       | Hennewig et al. 2008                            |

BWS the HH is usually transient and resolves spontaneously in a few days (Munns and Batch 2001). However a small number of patients (5% of cases), have persistent HH requiring medical therapy or even sub-total pancreatectomy.

Other causes of HH

An insulinoma is a rare cause of hyperinsulinism and must be considered in older children or adolescents presenting with HH (Shin et al. 2010). Insulinomas may be a part of multiple endocrine neoplasia syndrome type 1 (MEN1) and hence a family history may provide a diagnostic clue in the familial cases. Munchausen by proxy can present as factitious HH due to administration of insulin or anti diabetic drugs such as sulphonylureas. In some cases, this has led to misdiagnosis and consequent pancreatectomy (Giurgea et al. 2005).

Histological subtypes of hyperinsulinaemic hypoglycaemia

There are two major histological subtypes of CHI; diffuse and focal (Rahier et al. 2000). The diffuse form consists of hyper functioning pancreatic β-cells and affects the whole of pancreas. The most common causes of diffuse CHI are the recessive and dominant mutations in ABCC8 and KCNJ11. Patients with diffuse disease due to recessive mutations in ABCC8 and KCNJ11 do not usually respond to diazoxide.

The second histological subtype of CHI is the focal disease, which involves a small localised region of pancreas (2-10 mm in diameter). It is characterised by nodular hyperplasia of islet-like cell clusters, including ductuloin sol complex and giant β-cell nuclei surrounded by a histologically and functionally normal pancreatic tissue (Sempoux et al. 2004). The focal lesions can sometimes be deeply embedded within the pancreatic tissue.

The focal form has a distinctive genetic aetiology from that of the diffuse disease and involves two independent events, the first of which is the inheritance of a paternal mutation in ABCC8 or KCNJ11 (Verkarre et al. 1998). The second event is the somatic loss of the maternal 11p allele (11p15.1 to 11p15.5) involving the ABCC8 and KCNJ11 region within the focal lesion (De Lonlay et al. 1997). This paternal uniparental disomy unmasks the paternally inherited K_{ATP} channel mutation, which leads to altered expression of a number of imprinted genes, including the maternally expressed tumour suppressor genes H19 and CDKN1C, and the paternally expressed growth factor IGF2 (Fournet et al. 2001). These events eventually give rise to the increase in proliferation of β-cells evolving into a focal adenomatous hyperplasia. The focal disease is always sporadic in origin.

Clinical presentation of HH

HH most commonly presents in the newborn but it can also present during infancy and childhood. The clinical presentation of hypoglycaemia is most severe in the newborn and may be quite subtle in the infancy and childhood periods. The hyperinsulinaemic hypoglycaemia due to recessive mutations in ABCC8/KCNJ11 genes is usually refractory to oral feeds and requires high concentrations of intravenous glucose to maintain normoglycaemia (Aynsley-Green et al. 2000). However, the milder forms may be able to maintain normoglycaemia on oral feeds. Hypoglycaemic symptoms may vary from being non-specific (such as poor feeding, lethargy and irritability) to severe (such as apnoea, seizures or coma).

As a result of the fetal hyperinsulinaemia, newborns with CHI may be macrosomic however; the absence of macrosomia does not exclude CHI.

Hypertrophic cardiomyopathy and hepatomegaly (increased storage of glucose as glycogen) are observed in some patients with CHI. The mechanism of cardiomyopathy and hepatomegaly in these patients is unclear but might be related to the effect of fetal hyperinsulinaemia (Aynsley-Green et al. 2000).
Diagnosis of HH

The early diagnosis of HH is fundamentally important for preventing hypoglycaemic brain injury hence clinicians should have a low threshold for recognising these patients. Any patient with recurrent or persistent hypoglycaemia can potentially have HH and this is the only cause of hypoglycaemia which persists despite continuous administration of glucose. A powerful clue to the dysregulated insulin secretion is the calculation of the intravenous glucose infusion rate required to maintain normoglycaemia. An intravenous glucose infusion rate of >8 mg/kg/min (normal is 4-6 mg/kg/min) is virtually diagnostic of HH (Aynsley-Green et al. 2000). In milder forms of HH, it will be important to establish the duration of fasting and whether the hypoglycaemia is precipitated by meals (protein sensitivity) or by exercise.

In HH there is an inappropriate concentration of serum insulin (and/or c-peptide) for the level of blood glucose (spontaneous or provoked). The metabolic effect of this inappropriate insulin secretion is reflected by the inappropriately low levels of serum ketone bodies and fatty acids during the hypoglycaemic episode. There is no correlation between the serum insulin concentration and the severity of the hypoglycaemia (Palladino et al. 2008a, b). In some difficult cases the diagnosis of HH should not be based on an isolated serum insulin concentration but on the clinical presentation and the biochemical profile of insulin action (low beta-hydroxybutyrate and fatty acid concentrations). The diagnostic criteria for HI are summarised in Table 1.

An elevated serum ammonia concentration (appropriately collected and analysed) in a patient with HH is suggestive of the hyperinsulinism and hyperammonaemia (HI/HA) syndrome (Stanley et al. 1998). Raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate are diagnostic of a rare type of HI (hydroxyacetyl-Coenzyme A dehydrogenase (HADH) deficiency) (Clayton et al. 2001).

Some types of HH are elicited only after provoked testing. For example in patients who have the hyperinsulinism and hyperammonaemia syndrome (who have fasting as well as protein induced hypoglycaemia) protein/leucine loading precipitates hypoglycaemia (Hsu et al. 2001). The patients with exercise induced HH will require a formal exercise test and or a pyruvate load to demonstrate post exercise induced hypoglycaemia (Meissner et al. 2005; Otonkoski et al. 2003).

In some patients a positive glycaemic response (rise in the blood glucose concentration of >1.5 mmol/l) following an intramuscular/intravenous injection of glucagon at the time of hypoglycaemia provides supportive evidence (Finegold et al. 1980). A glycaemic response to a subcutaneous dose of octreotide may also aid diagnosis along with decreased serum levels of insulin growth factor binding protein 1 (IGFBP-1) as insulin suppresses the transcription of the IGFBP-1 gene (Levitt Katz et al. 1997).

Management

The early diagnosis and immediate meticulous management are the cornerstones for preventing brain injury in patients with HH. Once the diagnosis is established the priority is to maintain normoglycaemia (3.5-6 mmol/L). Given the biochemical basis (hypoketotic) of the hypoglycaemia it is recommended that a higher threshold of blood glucose concentration is used to intervene and blood glucose concentrations are maintained within the normal range (3.5–6 mmol/l) (Hussain et al. 2007). This often requires the insertion of a central venous catheter to deliver concentrated solutions of glucose intravenously. A combination of oral feeds with a glucose polymer (such as Maxijul or Polycal) and intravenous fluids can be used to provide the carbohydrates.

In an emergency situation where venous access is difficult to obtain, intramuscular glucagon (0.5-1 mg) can be administered in order to temporarily improve blood glucose concentrations (Aynsley-Green et al. 2000). Glucagon causes immediate release of glycogen stores from the liver and also has actions on gluconeogenesis, ketogenesis and lipolysis. However glucagon in high doses causes paradoxical insulin secretion, so patients receiving a glucagon bolus should have intravenous glucose infusion to prevent rebound hypoglycaemia. It can also be administered (alone or in combination with octreotide) as an intravenous or subcutaneous infusion to stabilise blood glucose concentrations in the acute management of infants with HH.

Diazoxide is the mainstay of medical therapy and is used as a first line drug (Aynsley-Green et al. 2000). It is a ligand of the $K_{ATP}$ which will activate intact $K_{ATP}$ channels reversing glucose-induced channel closure. Diazoxide is ineffective in diffuse CHI due to inactivating mutations in $ABCC8$ and $KCNJ11$ and in patients with focal CHI. Fluid retention and hypertrichosis are common side effects. The fluid retention is mostly observed in the neonatal period, and may cause cardiac failure. Hence the concurrent use of a thiazide diuretic to prevent fluid retention. However, routine use of thiazide diuretic is not necessary in older children when there is no evidence of fluid retention. Octreotide is used in the short and long term management of hyperinsulinaemic hypoglycaemia (Glaser et al. 1989). Tachyphylaxis has been observed on long term use of Octreotide (Thornton and Alter 1993). Recently, Laje et al. have described four cases of necrotising enterocolitis (NEC) over a period of 8 years amongst 192 infants treated with octreotide suggesting a potential link between octreotide and NEC (Laje et al. 2010). Hence, it is important to closely monitor the infants on octreotide for signs of NEC especially in the presence of...
other risk factors (Laje et al. 2010). Table 2 summarises the medical therapy for CHI.

The role of 18F-DOPA-PET in differentiating focal from diffuse CHI

Patients who are unresponsive to first line treatment with diazoxide need further investigations. In these patients it is essential to differentiate focal from diffuse disease as the surgical approaches are radically different. The precise preoperative localisation and limited surgical removal of the focal domain can cure the patient from hypoglycaemia. In contrast, patients with diffuse disease may require a near total pancreatectomy which will have life-long implications (high risk of diabetes mellitus, pancreatic exocrine insufficiency).

Rapid genetic analysis for mutations in ABCC8 and KCNJ11 allows for identification of the majority of patients with diffuse disease (homozygous or compound heterozygous mutations in ABCC8 and KCNJ11) (Christesen et al. 2007). Patients with a paternal mutation in ABCC8 and KCNJ11 (or those with no mutations in these genes) potentially have focal disease and thus will require further imaging

Assess Diazoxide response

Diazoxide responsive

Assess fasting tolerance and if appropriate for age then discharge

Diazoxide unresponsive

Rapid mutational analysis of ABCC8/KCNJ11 genes

If routine genetic analysis reveals paternal ABCC8/KCNJ11 gene mutations then 18F-DOPA-PET/CT SCAN may be indicated

18F-DOPA-PET/CT

Genetically confirmed diffuse disease (Homozygous/compound heterozygous ABCC8/KCNJ11)

High calorie and volume feeds

Octreotide therapy

Near total pancreatectomy

Surgical resection (laparoscopic if possible) of focal lesion potentially curing patient

General Follow up:
Growth and Development
Neurological
Genetic counselling

For patients who have undergone near total pancreatectomy need follow up for risk of diabetes mellitus and assessment of pancreatic exocrine function.

Generally patients with recessive ABCC8/KCNJ11 mutations do not respond to diazoxide and will require further investigations.

Fig. 2 Outline of the suggested diagnostic and management cascade of patients presenting with HH. The assessment of the response to diazoxide is critical in terms of planning further investigations.
studies. In the last few years a novel imaging technique (Fluorine-18-L dihydroxyphenylalanine positron emission tomography (18F-DOPA PET/CT)) has been developed that offers precise pre-operative localisation of the focal lesion, thus guiding the extent of surgical resection (Otonkoski et al. 2006). The uptake of the positron emitting tracer 18F-DOPA is increased in β-cells with a high rate of insulin synthesis and secretion compared to unaffected areas allowing visualisation of the focal lesion. The sensitivity for detecting focal lesions varies between 88 and 94% with a specificity of 100% (Hardy et al. 2007a, b). Figure 2 gives an overview of the management of patients with CHI.

Surgical management of CHI

The focal form of the disease requires a limited pancreatectomy whereas diffuse disease will require a near total pancreatectomy (Fékété et al. 2004). The operation is traditionally carried out with the open approach and is associated with peri and post-operative complications. The use of laparoscopy represents a new approach to the diagnosis and management of infants with CHI (Bax and van der Zee 2007). Near-total pancreatectomy is associated with a high incidence of diabetes mellitus and pancreatic exocrine insufficiency and hence reserved for those severe cases where all medical therapy has failed.

Medical management of diazoxide unresponsive diffuse CHI

Some infants with confirmed diffuse disease (genetically/ by 18F-DOPA-PET scanning) who fail to respond to diazoxide may be managed with long term subcutaneous octreotide injections in combination with frequent feeding (Glaser et al. 1989). The principle of this treatment is based on the fact that the hypoglycaemia in some patients gradually gets milder over time. A gastrostomy is recommend in some patients as this will allow the delivery of bolus and continuous overnight feeds. A long acting octreotide formulation has now been described in two patients (Modan-Moses et al. 2011).

Summary

HH occurs as a result of the unregulated secretion of insulin from pancreatic β-cells. The molecular basis of HH involves defects in key genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A and UCP2) which regulate insulin secretion. The advent of rapid genetic analysis, imaging with 18F-DOPA-PET/CT and new surgical techniques have changed the clinical approach to these complex patients.

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