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Arch. Dis. Child. published online 4 Feb 2009; doi:10.1136/adc.2008.148171

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Hyperinsulinaemic Hypoglycaemia

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Key words: Insulin, glucose KATP channels, Hypoglycaemia, Hyperinsulinism

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Abstract:
Hyperinsulinaemic Hypoglycaemia (HH) occurs as a consequence of unregulated insulin secretion from pancreatic β-cells. In the newborn period it is the most common cause of severe and persistent hypoglycaemia. As HH is a major risk factor for brain injury and subsequent neurodevelopment handicap, the identification, rapid diagnosis and prompt management of patients with HH is essential if brain damage is to be avoided. Advances in molecular genetics, radiological imaging techniques (such as Fluorine-18 L-3, 4-dihydroxyphenylalanine positron emission tomography, (18F)DOPA-PET) scanning) and laparoscopic surgery have completely changed the clinical approach to infants with the severe congenital forms of HH. This review gives an outline of the clinical presentation, the diagnostic cascade, the underlying molecular mechanisms and the management of HH with a particular focus on congenital forms of hyperinsulinism.
Introduction:

The inappropriate secretion of insulin from pancreatic β-cells in relation to the blood glucose concentration leads to hyperinsulinemic hypoglycaemia (HH). This is a major cause of persistent and recurrent hypoglycaemia in the neonatal and infancy period. As HH is associated with a high risk of epilepsy, cerebral palsy and neurological handicap, the rapid diagnosis and appropriate management of these patients are essential for preventing brain injury. Biochemically inappropriate insulin secretion drives glucose into insulin sensitive tissues (such as skeletal muscle, adipose tissue and the liver) and simultaneously inhibits glucose production (via glycolysis and gluconeogenesis), as well as suppressing fatty acid release and ketone body synthesis (inhibition of lipolysis and ketogenesis). This metabolic "footprint" of insulin action (hyperinsulinemic hypoglycaemia, with inappropriately low fatty acid and ketone body formation) forms the biochemical basis for why patients with HH have an increased risk of brain injury. The brain is not only deprived of its most important substrate (namely glucose) but also ketone bodies which form an alternative source of fuel.

HH may be congenital (congenital hyperinsulinism CHI), secondary to certain risk factors (such as maternal diabetes mellitus, birth asphyxia and intra-uterine growth retardation) or associated with developmental syndromes (such as Beckwith-Weidemann syndrome (BWS)) and rare metabolic conditions such as congenital disorders of glycosylation (CDG syndromes) (see table 1). The hypoglycaemia may be precipitated by fasting or by the ingestion of a protein meal and in some cases by exercise. The hypoglycaemia might occur in the postprandial period.

CHI is an extremely heterogeneous condition in terms of clinical presentation, histological subgroups and underlying molecular biology. The genetic basis of CHI involves abnormalities in key genes involved in regulating insulin secretion from β-cells. Mutations in seven different genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1 and HNF4A) have been described that lead to dysregulated insulin secretion. Histologically CHI has been classified into two major subgroups, diffuse (affecting the whole pancreas) and focal (being localised to a single region of the pancreas) disease. The focal forms of CHI can be completely cured by partial pancreatectomy whereas the diffuse form may require a near total pancreatectomy. Recent advances in imaging techniques (such as such as Fluorine-18 L-3, 4-dihydroxyphenylalanine positron emission tomography (¹⁸FDOPA-PET) scanning) allow precise pre-operative localisation of the focal lesion and in combination with laparoscopic surgery have changed the clinical approach to these patients. Both sporadic and familial forms of CHI are recognised with the sporadic form having an incidence of 1 in 50,000 and in those communities with high rates of consanguinity the incidence can be as high as 1 in 2,500. This review gives an overview of HH, its clinical presentation, the diagnostic cascade, summary of the molecular mechanisms and outlines the management of patients with different forms of HH focussing in particular on CHI.

Clinical presentation:

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 hypoglycaemia is usually refractory to oral feeds and normoglycaemia can only be maintained by giving large volumes of concentrated dextrose infusions. 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 are typically macrosomic (especially those with mutations in HNF4A-see later) however the absence of macrosomia does not exclude CHI. Fetal hyperinsulinaemia also accounts for the hypertrophic cardiomyopathy and hepatomegaly (increased storage of glucose as glycogen) that is commonly observed in patients with CHI.

Infants born to mothers with diabetes mellitus (insulin dependent or gestational), those who have sustained perinatal asphyxia and those with intrauterine growth restriction (IUGR) are at an increased
risk of developing HH.[5] The HH observed in these groups is sometimes referred to as “transient”. Most newborns with these risk factors will have HH that tends to last for a few days and then resolves. However from the clinical management point of view it is important to be aware that a subgroup of newborns with IUGR and perinatal asphyxia can have protracted or prolonged form of HH that requires treatment with diazoxide, persists for several months, and then resolves spontaneously.[6, 7]

At present it is not clear why some infants with perinatal asphyxia and IUGR have protracted HH. A large number of developmental syndromes may present in the newborn period with HH (see table 1). The most common syndrome associated with HH is BWS. 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.[8]. In the vast majority of patients with BWS the HH is usually transient and resolves spontaneously. However a small number of patients (5% of cases), have persistent HH requiring medical therapy or even sub-total pancreatectomy.[9]

HH may also present in the postprandial period for example in the “dumping syndrome”. The “dumping syndrome” is classically observed in infants following gastro-oesophageal surgery.[10] Some types of HH are elicited only after provocation testing. For example in patients who have the hyperinsulinism and hyperammonaemia syndrome (who also have fasting hypoglycaemia) protein/leucine loading precipitates hypoglycaemia. [11] Similarly in those patients with exercise induced hyperinsulinism, exercise provocation testing will cause hypoglycaemia after the exercise test.[12,13] A rare cause of post prandial hyperinsulinaemic hypoglycaemia is due to mutations in the insulin receptor gene. [14]

An insulinoma is a rare cause of HH and must be considered in older children or adolescents presenting with HH. 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.[15] 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.[16]

**Diagnosis:**

The early diagnosis of HH is fundamentally important for preventing hypoglycaemic brain injury, hence clinicians should have a low threshold for recognising patients with HH. Any patient with recurrent or persistent hypoglycaemia can potentially have hyperinsulinism. In the history it will be important to establish the duration of fasting and whether the hypoglycaemia is precipitated by meals (dumping syndrome, protein sensitivity) or by exercise. Typically newborns with HH have markedly reduced fasting tolerance (less than 1 hour).

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 >8mg/kg/min (normal is 4-6mg/kg/min) is virtually diagnostic of hyperinsulinism. Biochemically, HH is diagnosed by the demonstration of 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.[1] It is important to be aware that a ‘normal’ concentration of insulin is abnormal in the context of a low blood glucose concentration.[1] There is no correlation between the serum insulin concentration and the severity of the hypoglycaemia. In adults, β-cells are exquisitely sensitive to the prevailing blood glucose concentration such that insulin secretion is suppressed when the blood glucose concentration reaches around 4mmol/L.[17] In the neonatal period this fine tuning of insulin secretion to the blood glucose level is immature and not so tightly regulated.[18] Hence 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 counter-regulatory hormonal response
to hypoglycaemia is blunted in some infants with CHI with inappropriately low serum cortisol and glucagon level.[19, 20] The diagnostic criteria for HH are summarized in table 2.

The measurement of certain biochemical markers may provide a clue to the type of HH. An elevated serum ammonia concentration (appropriately collected and analysed) in a patient with HH is suggestive of the hyperinsulinism and hyperammonaemia syndrome.[21] Similarly a raised serum lactate concentration is found in some non-asphyxiated IUGR patients with HH.[22] Acylcarnitine analysis and urine organic acids should be performed in all patients with persistent HH as the demonstration of raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate are diagnostic of a rare type of CHI (hydroxyacyl-Coenzyme A dehydrogenase (HADH) deficiency).[23]

The diagnosis of some forms of HH will require provocation testing. For example patients with HH due to the “dumping” syndrome will require an oral glucose load and those with HH due to protein/leucine sensitivity will require loading with protein/leucine.[24, 11] In those patients with exercise induced HH a formal exercise test and or a pyruvate load will be required to demonstrate post exercise induced hypoglycaemia.[12, 13]

Some cases of CHI may be subtle and these will require more detailed evaluation. In some patients a positive glycaemic response (rise in the blood glucose concentration of >1.5mmol/l) following an intramuscular/intravenous injection of glucagon at the time of hypoglycaemia provides supportive evidence.[25] 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.[26]

Pathophysiology of CHI:

The pancreatic β-cell adenosine triphosphate-sensitive potassium channels (KATP channels) play a pivotal role in glucose stimulated insulin secretion. These channels are hetero-octameric complexes comprising of four inwardly rectifying potassium channel (Kir6.2) subunits and four of the sulphonylurea receptor 1 (SUR1) subunits. The channels couple glucose metabolism to membrane electrical activity and insulin release in pancreatic β-cells. Glucose metabolism leads to an increase in the intracellular ratio of ATP/ADP within the β-cell causing closure of the channels; this results in cell membrane depolarization, Ca2+ influx via voltage gated calcium channels and insulin exocytosis. Figure 1 outlines the role of the KATP channels in the pancreatic β-cell and summarises the known genetic causes of CHI.

The SUR1 and Kir6.2 proteins are encoded by the ABCC8 and KCNJ11 genes, respectively. Therefore, it is not surprising that the most common known cause of congenital hyperinsulinism (CHI) is loss of function mutations in these two genes.[27,28] These mutations either impair the ability of MgADP to stimulate channel activity, or affect the expression of the KATP channels at the surface membrane.[29,30] This results in continuous depolarisation of the β-cell membrane and dysregulated insulin secretion. The majority of KATP channel mutations have been known to act recessively. However, recent reports of autosomal dominantly inherited mutations in patients with CHI [31-34] suggest that they may be more common than recognised.

Heterozygous activating mutations have been reported in the glucokinase gene (GCK) in patients with CHI.[35] Glucokinase is the rate-limiting enzyme for glucose metabolism in the β-cell and hence is pivotal in regulating glucose-induced insulin secretion. Activating mutations cause an increased affinity of glucokinase for glucose with increased rates of glycolysis at low blood glucose concentrations. This increases insulin secretion independent of blood glucose concentration. The age of onset and severity of symptoms can vary markedly within families.[35-38] Progression to diabetes in later life has been described in a few of these patients suggesting that β-cell failure may be a sequel of the hyperinsulinism.[35]
Heterozygous mutations in the \textit{GLUD1} gene, which encodes the enzyme glutamate dehydrogenase (GDH), have been identified in patients with hyperinsulinism and hyperammonaemia (HI/HA Syndrome) with plasma ammonium levels being persistently raised to 3-8 times the upper limit of normal.[21] HI/HA syndrome typically causes protein sensitive hypoglycaemia, in addition to the fasting hypoglycaemia. [11] GDH is an intra-mitochondrial enzyme involved in protein (leucine)-mediated insulin release. In the \(\beta\)-cell leucine stimulates the release of insulin by allosterically activating GDH which results in increased oxidation of glutamate. \textit{GLUD1} mutations that impair inhibitory control of the enzyme by its allosteric inhibitor GTP, result in increased enzyme activity and ultimately increased insulin secretion. The mechanism by which \textit{GLUD1} mutations cause hyperammonaemia remains to be determined; however it is known that high levels of glutamate are required for the conversion of ammonium to urea in the liver.

\textbf{Recent advances in the genetics of congenital hyperinsulinism}

Recently, three further genetic aetiologies have been described in patients with CHI. Recessively inherited mutations in the \textit{HADH} gene which encodes the enzyme hydroxyacyl-Coenzyme A dehydrogenase (HADH), (previously known as Short-chain L-3-Hydroxyacyl-CoA dehydrogenase SCHAD), have been described in a few patients with CHI.[23] HADH catalyses the penultimate step in fatty acid \(\beta\)-oxidation in the mitochondria. Patients typically present with raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate levels.[39,40] The precise mechanism of dysregulated insulin secretion in patients with a HADH deficiency is not understood.

More recently, heterozygous loss-of-function mutations in the Hepatocyte Nuclear Factor 4A (\textit{HNF4A}) gene resulting in transient or persistent CHI,[41,42] and heterozygous gain-of-function mutations in the \textit{SLC16A1} gene which encodes the monocarboxylate transporter (MCT-1) causing physical exercise-induced hyperinsulinism (EIHI) [43] have been reported.

\textit{HNF4A} mutations are a cause of maturity-onset diabetes of the young (MODY). They result in progressive \(\beta\)-cell dysfunction, characterised by an inability to increase insulin secretion at high blood glucose levels. [44] These mutations are also associated with increased birth weight and macrosomia [41, 45] and some patients have neonatal hypoglycaemia. [41] The severity of hypoglycaemic episodes varies from diet-controlled neonatal hypoglycaemia to persistent hyperinsulinism requiring diazoxide treatment for a number of years. The mechanism by which \textit{HNF4A} mutations cause CHI is not known.

Patients with EIHI resulting from a \textit{SLC16A1} mutation have increased expression of the pyruvate and lactate transporter, MCT-1, within the pancreatic \(\beta\)-cell. Usually, reduced expression of MCT-1 renders the \(\beta\)-cell unresponsive to acute changes in the extracellular concentrations of lactate or pyruvate.[13] Activating mutation in the promoter region of \textit{SLC16A1} induce increased expression of MCT1 in the \(\beta\)-cell (where this gene is not usually transcribed) allowing pyruvate uptake and pyruvate-stimulated insulin release despite ensuing hypoglycaemia.[43] Patients with an \textit{SLC16A1} mutation usually present with symptoms of severe hypoglycaemia following strenuous exercise.

\textbf{Histology}

Two main histological subtypes have been described in patients with CHI. Focal pancreatic lesions appear as small regions of islet adenomatosis measuring 2-10mm which are characterised by \(\beta\)-cells with enlarged nuclei surrounded by normal tissue. In contrast diffuse pancreatic disease affects all the \(\beta\)-cells within the islets of Langerhans.[3] The histological form of CHI can be a guide as to the mode of inheritance. Diffuse disease can be familial or sporadic and can result from recessively inherited or dominantly acting mutations in the genes previously described whilst focal disease is always sporadic.[46]

Focal disease results from paternal uniparental disomy (UPD) encompassing chromosome11p15.5-11p15.1 within a single pancreatic \(\beta\)-cell which unmasks a paternally inherited K\text{\textsubscript{ATP}} channel mutation
at 11p15.1,[46,47] Paternal UPD at 11p15.5 causes altered expression of a number of imprinted genes, including the maternally expressed tumor suppressor genes H19 and CDKN1C, and the paternally expressed growth factor IGF2, likely leading to clonal expansion of the single cell and dysregulated insulin secretion from the resulting focal lesion.

A few patients have been reported to have ‘atypical histology’.[48] In one patient ‘atypical diffuse disease’ was shown to result from somatic mosaicism for segmental UPD 11 which unmasked a recessively acting ABCC8 mutation.[49] In the remaining patients the genetic aetiology remains unknown.

Management of HH:

Immediate 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 (3.5-6mmol/L). Given the biochemical basis (hypoketotic) of the hypoglycaemia it is recommended that a higher threshold of blood glucose concentration is used to intervene [50] and blood glucose concentrations are maintained within the normal range (3.5–6 mmol/l).[51] 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. Clinicians should not underestimate the complex management issues in patients with CHI and given the high propensity for brain injury it is recommended that the management of these patients is discussed with a tertiary centre and if required, transfer to the referral centre should be arranged.

In an emergency situation where venous access is difficult to obtain, intramuscular glucagon (0.5-1mg) can be administered in order to temporarily improve blood glucose concentrations. Glucagon causes immediate release of glycogen stores from the liver and also has actions on gluconeogenesis, ketogenesis and lipolysis.[52] However glucagon in high doses causes paradoxical insulin secretion,[53] so patients receiving a glucagon bolus should have intravenous glucose infusion to prevent rebound HH. It can also be administered (alone or in combination with octreotide) as an intravenous or subcutaneous infusion to stabilise blood glucose concentrations (table 3) in the acute management of infants with HH.

Prolonged periods of intravenous/nasogastric or gastrostomy feeding can hamper the ‘orality’ of infants with CHI and lead to difficulty in establishment of oral feeds. Furthermore, gastro-oesophageal reflux disease and foregut dysmotility are commonly observed in these infants; which often compounds the feeding problems.[54] Early treatment of reflux disease and introduction of oral feeds with avoidance of force-feeding is hence recommended. In severe cases, the expertise of a skilled speech and language therapist may be required to help establish a normal feeding pattern.

Further management

Further management involves assessing the response to different medical therapies. It is important to assess the response to each medication before moving onto the next one. Figure 1 shows the management cascade and table 3 outlines the medical therapies used.

The mainstay of medical therapy is diazoxide- a drug that binds to the intact SUR1 component of the K$_{ATP}$ channels. It acts by keeping the K$_{ATP}$ channels open, thereby preventing depolarisation of the ß-cell membrane and insulin secretion. In newborns it is used in conjunction with chlorothiazide, a diuretic with hyperglycaemic properties.[55] Diazoxide is effective in virtually all forms of HH except in diffuse CHI due to inactivating mutations in ABCC8 and KCNJ11 and in patients with focal CHI. However, there is one reported case of CHI due to a mutation in the GCK gene that was unresponsive to diazoxide. [37] Diazoxide has a potent fluid retaining action (especially in newborns) and hence it
must be used with caution especially in patients who are receiving large volumes of intravenous fluids/oral feeds.

**Diazoxide unresponsive CHI:**

The management of patients who are unresponsive to first line treatment with diazoxide has radically changed in the last a few years due to advances in molecular genetics, radiological imaging techniques and laparoscopic surgery. In patients that are unresponsive to diazoxide 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 “cures” the patient.[56] In contrast, patients with diffuse disease may require a near total pancreatectomy which will have lifelong implications (high risk of diabetes mellitus, pancreatic exocrine insufficiency).

Rapid genetic analysis for mutations in *ABCC8* and *KCNJ11* allows identification of the majority of patients with diffuse disease (homozygous or compound heterozygous mutations in *ABCC8* and *KCNJ11*). Patients with a paternal mutation in *ABCC8* and *KCNJ11* (or those with no mutations in these genes) potentially have a focal disease and thus will require further imaging studies with \(^{18}\text{F} \text{DOPA-PET}\) scan for precise pre-operative localisation of the focal lesion. Patients with genetically confirmed diffuse disease do not require further imaging studies. However it is important to be aware that mutational analysis may not be definitive in some cases. The principle of \(^{18}\text{F} \text{DOPA-PET}\) scan is based on the fact that pancreatic islets take up L-3, 4- dihydroxyphenylalanine (L-DOPA), and convert it to dopamine by DOPA decarboxylase, present in the islet cells. The uptake of the positron emitting tracer \(^{18}\text{F} \text{DOPA-PET}\) is increased in ß-cells with a high rate of insulin synthesis and secretion compared to unaffected areas.[57] allowing visualisation of the focal lesion. The sensitivity for detecting focal lesions varies between 88 and 94% with a specificity of 100%. [58, 59].

**Surgical management of CHI**

The focal form of the disease requires a limited pancreatectomy whereas diffuse disease will require a near total pancreatectomy.[60] The operation is traditionally carried out with the open approach and is associated with peri- and post-operative complications.[61] The use of laparoscopy represents a new approach to the diagnosis and management of infants with CHI.[62, 63, 64, 65] The laparoscopic approach has been used with success for removal of focal lesions,[63] especially in the area around the tail of the pancreas. Laparoscopic surgery is associated with less post-operative trauma and faster post-operative recovery in comparison with the traditional open approach.[62, 65] However, lesions in the head of the pancreas may not be amenable to this surgical approach. Laparoscopic subtotal pancreatectomy has been described in one patient with diffuse disease.[64] Near-total pancreatectomy is associated with a high incidence of diabetes mellitus and pancreatic exocrine insufficiency [66] 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 \(^{18}\text{F} \text{DOPA-PET}\) scanning) who fail to respond to diazoxide may be managed with long term subcutaneous octreotide injections in combination with frequent feeding. Octreotide is a long-acting analog of the natural hormone, somatostatin, which has inhibitory effects on the release of insulin from pancreatic ß-cells. It is used in the short and long term management of some patients with CHI. In the short term (with and without glucagon) it is used to stabilise patients pending further investigations. Octreotide has been successively used in the long term management of some CHI patients in combination with frequent feeding.[67] The principle of this treatment is based on the fact that the hypoglycaemia in some patients gradually gets milder over time. The long term medical management of diffuse disease with octreotide and frequent feeding should not be taken lightly as it may impose a huge burden and is extremely stressful on the family. A gastrostomy is recommend in these patients as this will allow the delivery of bolus and continuous overnight feeds.
Nifedipine is a calcium-channel antagonist and has been used in some patients with CHI although the vast majority of patients fail to show any response. Despite this there have been several reports of nifedipine responsive CHI patients [68, 69] but the underlying molecular pathophysiology of the CHI in these reported cases is unclear. Table 3 summarizes the dose, route of administration, side-effects and practical management tips for the use of the above drugs.

Conclusions

Hyperinsulinaemic hypoglycaemia is an important cause of hypoglycaemia in childhood. Early recognition and prompt, appropriate management are essential to avoid the neurological consequences associated with this condition. HH is an extremely heterogeneous condition. An understanding of the genetic mechanisms leading to the congenital forms of hyperinsulinism has begun to unravel the heterogeneity seen with this condition and has also provided novel insights into the mechanisms involved in insulin secretion. Recent advances in the fields of molecular genetics along with novel imaging techniques ($^{18}$FDOPA-PET scanning) and laparoscopic surgery have changed the clinical care of infants with CHI. However, the genetic aetiology of CHI is yet to be identified in 50% of the patients. Finally, treatment options for medically unresponsive diffuse CHI remain unsatisfactory (near total pancreatectomy) and continue to pose a management challenge.
Legends:

Figure 1: Schematic representation of the known causes of CHI. Loss of function mutations in the genes *KCNJ11* and *ABCC8* which encode the Kir6.2 (dark grey) and the SUR1 (light grey) subunits of the K\textsubscript{ATP} channel are the commonest cause of CHI. Gain of function mutations in the *GCK* and *GLUD1* (encoding GDH) genes have been described in patients with CHI. Whilst *SLC16A1* gene mutations which cause an increase in MCT-1 activity result in exercise-induced hyperinsulinism. The molecular mechanisms which lead to CHI in patients with *HADH* (encoding SCHAD) and *HNF4A* mutations remains to be determined.

Figure 2: Figure demonstrating the two major histological subgroups of CHI with the implicated genetic mechanisms. Diffuse CHI affects the entire pancreas while the focal form is localised to a single region of the pancreas.

Figure 3: Flow chart outlining the management cascade of neonates with hyperinsulinaemic hypoglycaemia. Clinically, HH can be classified into diazoxide responsive and diazoxide unresponsive disease. An \(^{18}\text{FDG}\) DOPA-PET scan is currently only indicated in neonates who are unresponsive to diazoxide and do not have genetically confirmed diffuse disease.

Table 1: Summary of the known causes of hyperinsulinaemic hypoglycaemia

Table 2: Diagnostic biochemical features of hyperinsulinaemic hypoglycaemia

Table 3: Summary of the medications used in the management of CHI
Table 1: Causes of Hyperinsulinaemic Hypoglycaemia:

<table>
<thead>
<tr>
<th>Causes of hyperinsulinaemic hypoglycaemia</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital Hyperinsulinism (Mode of inheritance)</strong></td>
<td></td>
</tr>
<tr>
<td>$ABCC8$ (Autosomal recessive and dominant)</td>
<td>27,29-33</td>
</tr>
<tr>
<td>$KCNJ11$ (Autosomal recessive and dominant)</td>
<td>28,33,34</td>
</tr>
<tr>
<td>$GLUD1$ (Dominant)</td>
<td>21</td>
</tr>
<tr>
<td>$GCK$ (Dominant)</td>
<td>35-38</td>
</tr>
<tr>
<td>$HADH$ (Recessive)</td>
<td>23,39,40</td>
</tr>
<tr>
<td>$HNF4A$ (Dominant)</td>
<td>41,42,45</td>
</tr>
<tr>
<td>$SLC16A1$ (Exercise induced) (Dominant)</td>
<td>43</td>
</tr>
<tr>
<td><strong>Secondary to (usually transient)</strong></td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes mellitus (gestational and insulin dependent)</td>
<td>5,6,7</td>
</tr>
<tr>
<td>IUGR</td>
<td>5,7</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
<td>70</td>
</tr>
<tr>
<td>Rhesus isoimmunisation</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital disorders of glycosylation (CDG), Type 1a/b/d</td>
<td>71-73</td>
</tr>
<tr>
<td>Tyrosinaemia type I</td>
<td>74</td>
</tr>
<tr>
<td><strong>Associated with Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>Beckwith-Wiedemann</td>
<td>7,8</td>
</tr>
<tr>
<td>Soto</td>
<td>75</td>
</tr>
<tr>
<td>Kabuki</td>
<td>76</td>
</tr>
<tr>
<td>Usher</td>
<td>77</td>
</tr>
<tr>
<td>Timothy</td>
<td>78</td>
</tr>
<tr>
<td>Costello</td>
<td>79</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>80</td>
</tr>
<tr>
<td>Mosaic Turner</td>
<td>81</td>
</tr>
<tr>
<td>Central Hypoventilation Syndrome</td>
<td>82</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
<td></td>
</tr>
<tr>
<td>Dumping syndrome</td>
<td>9</td>
</tr>
<tr>
<td>Insulinoma (sporadic or associated with MEN Type 1)</td>
<td>14</td>
</tr>
<tr>
<td>Insulin gene receptor mutations</td>
<td>10</td>
</tr>
<tr>
<td>Factitious HH (Munchausen-by-proxy)</td>
<td>15</td>
</tr>
</tbody>
</table>
Table 2: Diagnostic biochemical features of hyperinsulinaemic hypoglycaemia:

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose infusion rate &gt;8 mg/kg/min</td>
</tr>
<tr>
<td>Laboratory blood glucose &lt;3 mmol/l with</td>
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<tr>
<td>- detectable serum insulin/C-peptide</td>
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<td>- suppressed/low serum ketone bodies</td>
</tr>
<tr>
<td>- suppressed/low serum fatty acids</td>
</tr>
<tr>
<td>- suppressed branch chain amino acids</td>
</tr>
<tr>
<td>Serum ammonia level may be raised (HI/HA syndrome)</td>
</tr>
<tr>
<td>Raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate (HADH deficiency)</td>
</tr>
<tr>
<td>Supportive evidence (when diagnosis is in doubt):</td>
</tr>
<tr>
<td>Positive glycaemic (&gt;1.5mmol/L) response to intramuscular/ intravenous glucagon</td>
</tr>
<tr>
<td>Positive glycaemic response to a subcutaneous/intravenous dose of octreotide</td>
</tr>
<tr>
<td>Low levels of serum IGFBP1</td>
</tr>
</tbody>
</table>
### Table 3: Medications used in the treatment of CHI:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route of administration</th>
<th>Side effects</th>
<th>Practical management points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazoxide</td>
<td>5-20mg/kg/day, divided into three doses</td>
<td>Oral</td>
<td>Common: fluid retention, hypertrichosis Others: hyperuricaemia, eosinophilia, leukopaenia.</td>
<td>Use in conjunction with chlorothiazide especially in newborns. Restrict fluid intake, especially on the higher doses. Carefully monitor fluid balance.</td>
</tr>
<tr>
<td>Chlorothiazide (in conjunction with diazoxide)</td>
<td>7-10mg/kg/day, divided into two doses</td>
<td>Oral</td>
<td>Hyponatraemia, hypokalaemia</td>
<td>Monitor serum electrolytes. Monitor blood pressure. Not effective in patients with CHI due to defective K\textsubscript{ATP} channels.</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>0.25-2.5mg/kg/day, divided into three doses</td>
<td>Oral</td>
<td>Hypotension</td>
<td>Monitor blood pressure. Not effective in patients with CHI due to defective K\textsubscript{ATP} channels.</td>
</tr>
<tr>
<td>Glucagon</td>
<td>1-20μg/kg/hr, 0.5-1mg for emergency treatment of hypoglycaemia</td>
<td>SC/IV infusion, IM/IV</td>
<td>Nausea, vomiting, skin rashes. Paradoxical hypoglycaemia in high doses</td>
<td>Avoid high doses. Watch for rebound hypoglycaemia when used as an emergency treatment for hypoglycaemia.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>5-30μg/kg/day, SC/IV as a continuous infusion or 6-8 hourly injections</td>
<td>SC/IV as a continuous infusion or 6-8 hourly injections</td>
<td>Common: tachyphylaxis Others: Suppression of GH, TSH, ACTH, glucagon; diarrhoea, steatorrhoea, cholelithiasis, abdominal distension, growth suppression</td>
<td>Use with caution in infants at risk of necrotising enterocolitis, (reduces blood flow to the splanchnic circulation). Follow-up with serial ultrasound scans of the biliary tree, if on long-term treatment with octreotide. Monitor long-term growth.</td>
</tr>
</tbody>
</table>
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References:


α-Ketoglutarate + NH₃

K⁺

$K_{ATP}$ channel

Voltage-gated calcium channel

$Ca^{2+}$

Pyruvate

$\alpha$-Ketoglutarate + NH₃

Increased MCT-1 activity

Increased GDH activity

Glutamate

Glucose-6-phosphate

Glucose

Glutamine

Leucine

Increased GCK activity

Insulin granule exocytosis

$ATP/ADP$

$K^+$

Loss of $K_{ATP}$ channel function

Loss of function of SCHAD

Loss of HNF4A function

Abnormal Metabolites

Fatty Acids

Increased MCT-1 activity

Increased GDH activity

Increased GCK activity

Loss of function of SCHAD

Loss of HNF4A function

Abnormal Metabolites
Diffuse disease:
• Entire pancreas is affected
• Associated with mutations in ABCC8/ KCNJ11/ GCK/ GLUD1/ HNF4A/HADH and SLC16A1

Focal disease:
• A focal area of the pancreas is affected
• Associated with a paternal mutation in ABCC8 or KCNJ11 and paternal UPD encompassing 11p5.1 to 11p15.5 in the focal area
Established diagnosis of HH

Diazoxide responsive (1)

Assess fasting tolerance and discharge

Follow-up:
Request genetic analysis on the basis of the phenotype
Consider trial off diazoxide in hospital when dose of diazoxide falls below 5mg/kg/day
Regular monitoring of growth/development and neurology

Diazoxide unresponsive

Rapid genetic analysis of the ABCC8 and KCNJ11 genes

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

No

18F-DOPA-PET/CT scan

Focal Disease

Resection of focal lesion

Follow up:
Regular monitoring of growth, development and neurology

Diffuse Disease

High calorie diet/frequent feeds
Octreotide therapy
Near total pancreatectomy

Follow up:
Growth and Development
Neurological
Genetic counselling
Post near total pancreatectomy:
Diabetes mellitus management
Pancreatic exocrine function

Yes