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## Congenital Hyperinsulinism

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### 1. Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent and recurrent hypoglycaemia in neonates and infants during their first year of lives. CHI may lead to severe mental retardation and epilepsy if not treated properly. Both sporadic and familial variants of CHI are recognized, and of which sporadic forms is relatively uncommon (incidence 1 per 35,000 live births), comparing with the highly consanguineous familial forms high rates of consanguinity; with incidence may be as high as 1 in 2,500 live births in the corresponding communities. The clinical severity of CHI varies mainly with age of onset of hypoglycaemia (severe hypoglycaemia in neonates) and is remarkably predictive in terms of therapeutic outcome and genetic counseling.

### 2. Physiopathology of hypoglycemia

Hypoglycemia in children is defined by a glucose plasma level below 2.8 or 3 mmol/l, It is a life-threatening condition that requires being diagnosed and treated promptly and appropriately to avoid brain damage and general distress. Congenital hyperinsulinism is due to an inappropriate insulin over-secretion by the  $\beta$ -cells. Insulin is known to be the only hormone to decrease plasma glucose level, and the function of which is realized by inhibiting hepatic glycogenolysis and boosting muscle uptake as well as reducing lipolysis and ketogenesis. Mechanisms above might explain the major characteristic clinical findings of neonatal hyperinsulinism (HI): the increased glucose requirement to correct hypoglycemia, the responsiveness to exogenous glucagon, and the absence of ketone bodies detected.

Several pathways are involved in the regulation of insulin secretion by the pancreatic  $\beta$ -cell, helping explaining the effectiveness of diazoxide, somatostatin, calcium channel inhibitors and protein restricted diet treatments (Fig. 1). Glucose and other substrates, such as amino acids, stimulate insulin secretion, by raising the intracytosolic ATP/ADP ratio. Glucokinase enzyme initiates the  $\beta$ -cell glucose metabolism. It has a high  $K_m$  for glucose so that the blood concentration of glucose directly determines the rate in glucose oxidation of  $\beta$ -cell and

subsequently controls the insulin release. The increase in the cytosolic ATP/ADP ratio activates the plasma membrane sulfonylurea receptor 1 (SUR1), leading to the closure of the potassium channel ( $K_{ATP}$  channel) which depolarizes the plasma membrane and opens a voltage dependant calcium channel. The calcium cellular concentration consequently increases, which triggers the release of insulin from storage granules. Leucine, one of the most potent amino acids in stimulating insulin secretion, acts indirectly as a positive allosteric affector of glutamate dehydrogenase (GDH) which catalyses the oxidative deamination of glutamate to alpha-ketoglutarate and ammonia, using NAD or NADP as co-factor. Hyperactivation of GDH is responsible for an increased alpha of the  $\beta$ -cell ATP/ADP ratio. Diazoxide blocks insulin secretion by activating (opening) the SUR1. Somatostatin analogues act by inhibiting the insulin release through different mechanisms involving adenylyl cyclase and protein kinase A, and dietary protein restriction decreases the stimulation of GDH by leucine

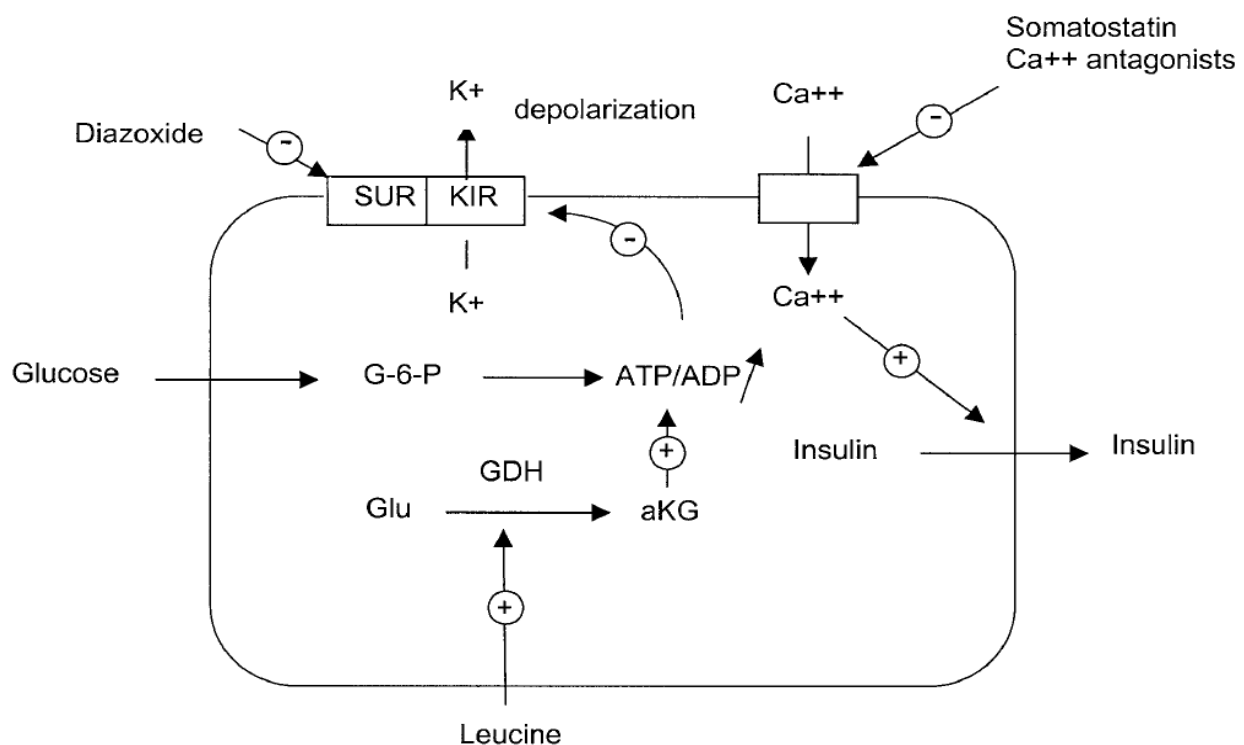


Fig. 1. Mechanisms of insulin secretion by the pancreatic beta cell. +: stimulation; -: inhibition; ADP: adenosine diphosphate; ATP: adenosine triphosphate;  $\alpha$ -KG:  $\alpha$ -ketoglutarate; G-6-P: glucose-6-phosphate; GDH: glutamate dehydrogenase.

### 3. Genetics

Insulin secretion from  $\beta$ -cells is precisely regulated to maintain plasma glucose levels within a normal range (3.5–5.5 mmol/l). The genetic basis of CHI involves defects in key genes which regulate insulin secretion from  $\beta$ -cells. The most common cause of CHI are recessive inactivating mutations in ABCC8 and KCNJ11 which encode the two subunits of the adenosine triphosphate sensitive potassium channels (ATP sensitive  $K_{ATP}$  channels) in the

pancreatic  $\beta$ -cell. These  $\beta$ -cell  $K_{ATP}$  channels play a key role in transducing signals derived from glucose metabolism to  $\beta$ -cell membrane depolarisation and regulated insulin secretion. Another recessive form of CHI is due to mutations in HADH (encoding for 3-hydroxyacyl-coenzyme A dehydrogenase). Dominant forms of CHI are due to inactivating mutations in ABCC8 and KCNJ11 and activating mutations in GLUD1 (encoding glutamate dehydrogenase), GCK (encoding glucokinase), HNF4A (encoding hepatocyte nuclear factor 4a) and SLC16A1 (encoding monocarboxylate transporter 1). Mutations in all these genes account for about 50% of the revealed causes of CHI, and in some populations mutations in these genes contributes to only about 20% of CHI cases, suggesting other novel genetic aetiologies. Table 1 summarises the known genetic causes of CHI.

Gene	locus	OMIM	Protein	Mechanism
ABCC8	11p15.1	600509	Sulfonylurea receptor1 (SUR1)	Defects in $K_{ATP}$ biogenesis and turnover, trafficking and nucleotide regulation
KCNJ11	11p15.1	600937	Inward rectifying potassium channel (Kir6.2)	Defects in $K_{ATP}$ biogenesis and turnover, trafficking and nucleotide regulation
GLUD1	10q23.3	138130	Glutamate dehydrogenase (GDH)	Loss of inhibition of GDH by GTP and increased basal GDH activity
GCK	7p15-13	138079	Glucokinase	Increased affinity of GCK for glucose
HADH	4q22-26	601609	3-hydroxyacyl-CoA dehydrogenase	Unknown
SLC16A1	1p13.2-p12	600682	Monocarboxylate transporter 1 (MCT1)	Increased expression of MCT1
HNF4A	20q12-13.1	600281	Hepatocyte nuclear factor 4 alpha	Unknown

Table 1. The genes implicated in congenital hyperinsulinism with the gene loci and proteins affected

### 3.1 Role of pancreatic $\beta$ -cell $K_{ATP}$ channels in glucose-induced insulin secretion

$K_{ATP}$  channels have a key role in the physiology of many cells, and defects in either structure or regulation is pathogenic. Functionally  $K_{ATP}$  channels provide a means of linking the electrical activity of a cell to its metabolic state by sensing changes in the concentration of intracellular nucleotides, and in some cases they mediate the actions of hormones and transmitters. The pancreatic  $K_{ATP}$  channel is a functional complex of the sulfonylurea receptor 1(SUR1) and an inward rectifier potassium channel subunit (Kir6.2) and acts pivotally in regulating insulin secretion from the  $\beta$ -cell. The Kir6.2 forms the pore of the channel and the SUR1 (an ATP binding cassette transporter) acts as a regulatory subunit.

$K_{ATP}$  channels are regulated by adenine nucleotides to convert changes in cellular metabolic levels into membrane excitability. Each subunit of the  $K_{ATP}$  channel is known to be regulated differentially. The Kir6.2 subunit determines the biophysical properties of the channel complex including  $K^+$  selectivity, rectification, inhibition by ATP and activation by acyl-CoAs. The sulfonylurea receptors endow  $K_{ATP}$  channels with sensitivity to the stimulatory actions of Mg-nucleotides and  $K_{ATP}$  channel openers (for example, diazoxide, nicorandil) and the inhibitory effects of sulfonylureas and glinides and endosulfins.

$K_{ATP}$  channels can only function if they are assembled and correctly transported to the cell membrane surface (trafficking). The assembly and trafficking of  $K_{ATP}$  channels are intricately linked processes. Only octameric  $K_{ATP}$  channel complexes are capable of expressing on the cell membrane surface. For example both Kir6.2 and SUR1 possess an endoplasmic reticulum (ER) retention signal (RKR) that prevents the trafficking of each subunit to the plasma membrane in the absence of the other subunit. Correct assembly of the two subunits masks these retention signals, allowing them to traffic to the plasma membrane. The retention signal is present in the C-terminal region of Kir6.2 and in an intracellular loop between TM11 and NBF-1 in SUR1. Truncation of the C-terminus of Kir6.2 deletes its retention signal, allowing functional expression of Kir6.2 in the absence of SUR1 subunit. In addition to these retrograde signals, the C-terminus of SUR1 has an anterograde signal, composed in part of a dileucine motif and downstream phenylalanine, which is required for  $K_{ATP}$  channels to exit the ER/cis-Golgi compartments and transit to the cell surface. Deletion of as few as seven amino acids, including the phenylalanine, from SUR1 markedly reduces surface expression of  $K_{ATP}$  channels. Thus, one function of SUR is as a chaperone protein, to facilitate the surface expression of Kir6.2. There is also some evidence that Kir6.2 provides a reciprocal service for SUR.

### 3.2 Mutations that affect $K_{ATP}$ channels in pancreatic $\beta$ -cells

The commonest genetic causes of CHI are autosomal recessive mutations in ABCC8 and KCNJ11 genes encoding the two subunits of the pancreatic  $\beta$ -cell  $K_{ATP}$  channels. Autosomal dominant mutations have also been described. These mutations result in differing abnormalities of recombinant  $K_{ATP}$  channels including protein folding, protein synthesis defects, assembly and trafficking defects, and alterations in both nucleotide regulation and open-state frequency.

The SUR1 and Kir6.2 proteins are encoded by adjacent genes (ABCC8 and KCNJ11, respectively) located on chromosome 11p15.1. Recessive inactivating mutations in ABCC8 and KCNJ11 cause the most common and most severe forms of CHI. Patients with mutations in these genes are usually unresponsive to medical therapy and may require pancreatectomy. Autosomal-dominant mutations in ABCC8 and KCNJ11 cause mild, medically responsive HH. In general, mutations in ABCC8 and KCNJ11 account for approximately 50% of the cases of CHI.

Recessive inactivating mutations in ABCC8 and KCNJ11 are typically associated with the diffuse type of CHI. Typical diffuse disease is characterized by enlarged nuclei of pancreatic  $\beta$ -cells, although the degree of nuclear enlargement might show variation from one islet to another. Other changes in the  $\beta$ -cells include an increase in quantity of proinsulin in the Golgi area and an increased amount of cytoplasm. By contrast, the focal form of the disease is characterized by the presence of adenomatous hyperplasia confined to a single region of the pancreas. In the majority of cases this hyperplasia is macroscopically invisible; loci can be 2–10 mm in diameter.

The genetic basis of focal disease involves the paternal inheritance of a recessive *ABCC8* or *KCNJ11* mutation and the somatic loss of heterozygosity in the distal portion of the short arm of the maternal chromosome 11. Somatic loss of heterozygosity represents the loss of normal function of one allele of a gene, the other allele of which was already inactivated in a cell (in this case, a pancreatic  $\beta$ -cell). Patients with focal, congenital HH might have more than one focal pancreatic lesion, which can be caused by a separate somatic maternal deletion of the 11p15.1 region. Focal lesions are different from insulinomas (which are also called adenomas) in terms of their histology and molecular mechanisms of insulin secretion.

### 3.3 Mutations that affect leucine and glucose metabolism in pancreatic $\beta$ -cells

Metabolopathies cause CHI either by altering the concentration of intracellular signalling molecules (such as ATP/ADP) or by the accumulation of intermediary metabolites. Autosomal dominant mutations in the genes encoding glutamate dehydrogenase (GDH) (*GLUD1*) and glucokinase (GCK) lead to inappropriate insulin secretion by increasing the amount of ATP in the  $\beta$ -cells. More recently autosomal recessive mutations in short-chain L-3-hydroxyacyl-CoA dehydrogenase (*HADHSC*) have been linked to defects in fatty acid oxidation and hyperinsulinism.

#### 3.3.1 Gain of function mutations in glutamate dehydrogenase

The *GLUD1* gene is located on chromosome 10q23.3 and contains 13 exons coding for a 505 amino acid mature enzyme, glutamate dehydrogenase (GDH). This enzyme catalyses the oxidative deamination of glutamate to  $\alpha$ -ketoglutarate and ammonia using NAD<sup>+</sup> and/or NADP<sup>+</sup> as co-factors. In the  $\beta$ -cells  $\alpha$ -ketoglutarate enters the tricarboxylic acid cycle and leads to an increase in the cellular ATP concentration. This increases the ATP/ADP ratio which triggers closure of the  $K_{ATP}$  channels and depolarisation of the  $\beta$ -cell membrane. This, in turn, opens the voltage gated calcium channel, raises the cytosolic calcium, and triggers the release of insulin.

Activating mutations (heterozygous missense single amino acid substitutions) in the *GLUD1* gene are the second most common cause of CHI. *GLUD1* gene mutations cause a form of CHI in which affected children have recurrent symptomatic HH together with a persistently elevated plasma ammonia value, the hyperinsulinism/hyperammonaemia (HI/HA) syndrome. The mutations causing HI/HA reduce the sensitivity of the enzyme to allosteric inhibition by the high energy phosphate GTP and in rare cases increase basal GDH activity. The loss of inhibition by GTP increases the rate of oxidation of glutamate in the presence of leucine, thereby increasing insulin secretion. The clinical picture is hence characterised by postprandial hypoglycaemia following a protein meal (fasting hypoglycaemia may also occur). The hypoglycaemia in patients with HI/HA syndrome is usually responsive to medical treatment with diazoxide. The hyperammonaemia is considered to be asymptomatic and hence efforts to reduce plasma ammonia values with sodium benzoate or N-carbamylglutamate do not seem to be beneficial.

#### 3.3.2 Congenital hyperinsulinism due to gain of function mutations in glucokinase

Heterozygous inactivating mutations in GCK cause maturity onset diabetes of the young (MODY), homozygous inactivating in GCK mutations result in permanent neonatal diabetes, whereas heterozygous activating GCK mutations cause CHI. So far seven activating GCK mutations (V455M, A456V, Y214C, T65I, W99R, G68V, S64Y) have been

described that lead to CHI. Activating GCK mutations increase the affinity of GCK for glucose and alter (reset) the threshold for glucose stimulated insulin secretion. All reported activating mutations cluster in a region of the enzyme, which has been termed the allosteric activator site and is remote to the substrate binding site. The allosteric site of GCK is where small molecule activators bind, suggesting a critical role of the allosteric site in the regulation of GCK activities. There is no evidence to suggest that over-expression of GCK (increased gene dosage effect) is a likely cause of CHI.

The clinical symptoms and course of patients with GCK mutations cover a broad spectrum from asymptomatic hypoglycaemia to unconsciousness and seizures, even within the same family with the same mutation, implicating a complex mechanism for GCK regulation. Patients with activating GCK mutations may present with postprandial hyperinsulinaemic hypoglycaemia. Most of the GCK mutations reported to date cause mild diazoxide responsive CHI.

### **3.4 Mutations in the HNF4A gene**

Heterozygote mutations in the human HNF4A gene classically lead to maturity onset diabetes of the young subtype 1 (MODY1), which is characterised by autosomal dominant inheritance and impaired glucose stimulated insulin secretion from pancreatic  $\beta$ -cell. These mutations in the HNF4A gene cause multiple defects in glucose stimulated insulin secretion and in expression of HNF4A dependent genes. Recently mutations in the HNF4A gene were reported to cause macrosomia and both transient and persistent HH. In one retrospective study the birth weight of the HNF4A mutation carriers compared to non-mutation family members was increased by a median of 790 g. Transient hypoglycaemia was reported in 8/54 infants with heterozygous HNF4A mutations and documented HH in three cases.

### **3.5 Mutations that cause defective fatty-acid metabolism in pancreatic $\beta$ -cells**

Loss-of-function mutations in the HADH gene are associated with CHI. The clinical presentation of all patients reported is heterogeneous, with either mild late onset intermittent HH or severe neonatal hypoglycaemia. All reported cases have presented with increased 3-hydroxyglutarate in urine and hydroxybutyrylcarnitine in blood which may be diagnostically useful markers for HADH deficiency. In the first patient reported sequencing of the HADH genomic DNA from the fibroblasts showed a homozygous mutation (C773T) changing proline to leucine at amino acid 258. Analysis of blood from the parents showed they were heterozygous for this mutation. Western blot studies showed undetectable levels of immunoreactive HADH protein in the patient's fibroblasts.

The molecular mechanism of how loss of function in the HADH gene leads to unregulated insulin secretion is still unclear. Several recent studies in rodents have begun to give some insights into how HADH regulates insulin secretion and its interaction with other genes involved in  $\beta$ -cell development and function. The normal  $\beta$ -cell phenotype is characterised by a high expression of HADH and a low expression of other  $\beta$ -oxidation enzymes. Downregulation of HADH causes an elevated secretory activity suggesting that this enzyme protects against inappropriately high insulin values and hypoglycaemia. Hence, HADH seems to be a negative regulator of insulin secretion in  $\beta$ -cells. Further studies will be required to understand fully the biochemical pathways by which defects in HADH lead to dysregulated insulin secretion.

#### 4. Histology

Two major histological forms of CHI have been described (diffuse and focal), there are still some cases which represent a diagnostic challenge, as they cannot be easily classified into focal or diffuse. Both the diffuse and focal forms share a similar clinical presentation, but result from different pathophysiological and molecular mechanisms. The histological form of CHI can be a guide as to the mode of inheritance, diffuse CHI usually presents as an autosomal recessive disorder, whereas focal CHI is sporadic.

The typical diffuse form affects all the  $\beta$ -cells within the islets of Langerhans and is most commonly due to recessive mutations in the genes encoding the two subunits of the  $K_{ATP}$  channel. Typical diffuse disease is characterized by an increase in the size of the pancreatic  $\beta$ -cell nuclei throughout the pancreas.

The 'focal' form (focal adenomatous pancreatic hyperplasia) of CHI is found in about 40–50% of the children and appears to be localized to one region of the pancreas. Focal pancreatic lesions appear as small regions of islet adenomatosis measuring 2–10 mm, which are characterized by  $\beta$ -cells with enlarged nuclei surrounded by normal tissue. Focal disease results from paternal uniparental disomy (UPD) encompassing chromosome 11p15.5–11p15.1 within a single pancreatic  $\beta$ -cell which unmasks a paternally inherited  $K_{ATP}$  channel mutation at 11p15.1. In addition, the lesion exhibits a somatic loss of a part of the maternally inherited chromosome 11p which includes imprinted maternally expressed tumour suppressor genes (H19 and P57 KIP2), paternally expressed insulin growth factor-2, as well as (non-imprinted) SUR1/Kir6. This results in a corresponding reduction to homozygosity of the paternal mutation, and the outcome is unregulated insulin secretion.  $\beta$ -cells within the focal lesion do not express p57 KIP2, but insulin growth factor-2 is mildly increased. The somatic loss of heterozygosity is associated with increased proliferation. The focal lesion is different from the insulinoma (also called adenoma) in histology and molecular mechanisms of insulin secretion.

#### 5. Clinical presentation

CHI typically presents in the first few days after birth in term and preterm infants with symptomatic hypoglycaemia. The patients may present with non-specific symptoms of hypoglycaemia such as poor feeding, lethargy, and irritability or symptoms such as seizures and coma. In CHI a blood sample taken at the time of hypoglycaemia will show an inappropriately raised serum insulin level with low serum fatty acid levels and ketone bodies. Most infants with hyperinsulinism present within the early neonatal period although infantile and childhood onset forms are also recognized. Transient hyperinsulinism is seen in association with maternal diabetes, birth asphyxia, polycythaemia, and rhesus incompatibility. Other syndromic associations which might be evident at birth include Beckwith syndrome, Sotos' syndrome, Perlman's syndrome, and the clinical phenotype characteristic of phosphomannose isomerase deficiency (carbohydrate-deficient glycoprotein syndrome type 1b).

Most neonates with HI are born at term and are either normal or large for gestational age, although HI is described in preterm infants. Many of these infants are overtly macrosomic and plethoric and may have characteristic facial appearances comprising high forehead, small nasal tip, and short columella giving the impression that the nose is large and bulbous, smooth philtrum, and thin upper lip. The key events in early neonatal management of



infants with HI involve avoidance of hypoglycaemia and careful definition of clinical and biochemical phenotype. Infants with severe HI will not uncommonly have glucose requirements of 15–20 mg/kg/min and as such will usually be dependent upon intravenous glucose infusions. Blood sugar concentrations are usually very labile and it is of paramount importance that venous access is secure in these cases—usually necessitating placement of a central venous catheter. Infants with persistent forms of HI should normally be assessed in a referral centre for HI which has the necessary resource for timely definition of clinical and biochemical phenotype, genotype, and, if appropriate, structural phenotype. The main differential diagnosis of congenital HI remains the factitious hyperinsulinism secondary to Munchausen by proxy syndrome, one of the parents administering insulin or sulfonylurea surreptitiously to their own child. Another period of onset for HI occurs later in infancy, between 1 and 20 months of life and is revealed in half of the patients by seizures. Macrosomy at birth can be noted. The characteristics of hypoglycemia are similar, although lower rates of intravenous glucose are required.

## 6. The diagnostic criteria for HI

The diagnostic criteria for congenital HI include: i) fasting and post-prandial hypoglycemia (<2.5–3 mmol/l) with unsuppressed insulin secretion (plasma insulin concentrations >1 mU/l), ii) a positive response to the subcutaneous or intramuscular administration of glucagon (plasma glucose concentration increase by 2 to 3 mmol/l following a 0.5 mg glucagon subcutaneous injection), iii) negative ketone bodies in urine (and in plasma) and iv) prolonged dependence on treatment to prevent hypoglycemia throughout the first months/years of life. Nevertheless, in infancy and childhood, normal plasma insulin and C-peptide concentrations during hypoglycemia do not exclude the diagnosis of HI and measurements have to be repeated. In the absence of clearly abnormal insulin levels during hypoglycemic episodes, an 8 to 12 hours fasting test aiming at revealing inappropriately low levels of ketone bodies, free fatty acid and branched chain amino acids can be helpful.

In some patients with protein-sensitive congenital HH owing to *GLUD1* mutations, a leucine provocation test might be required to demonstrate HH. Analyses of urinary organic acids and acylcarnitine should also be performed, as results could aid in the diagnosis of *HADH* deficiency. Serum glucagon levels are decreased in congenital HH. Patients with HH demonstrate a positive glycemic response (a rise in blood glucose level of >1.5 mmol/l) to intramuscularly or intravenously administered glucagon during times of hypoglycemia. Decreased serum levels of insulin-like growth-factor binding protein 1 (*IGFBP-1*) aid the diagnosis in some patients, because insulin suppresses transcription of the *IGFBP1* gene. Patients with exercise-induced HH will require an exercise provocation test and/or a pyruvate load to induce hypoglycemia.

All new HI patients should be screened for hyperammonemia to diagnose the HI/HA syndrome (*GLUD1* gene), for short chain hydroxyacyl-CoA dehydrogenase (*SCHAD*) deficiency (*HADH* gene) with urine organic acids and plasma acylcarnitines chromatographies, and for CDG syndromes, as these 3 diseases may present in the neonatal period as apparently isolated HI. Other genes can be suspected depending on the context. *SLC16A1* gene will be analyzed in case of Exercise-induced hyperinsulinism (EIHI), *HNF4A* gene when the newborn is macrosomic with a family history of MODY diabetes. Finally, familial forms or consanguinity and syndromic forms have to be checked as these are associated with a diffuse HI.

## 7. Medical management

Rapid diagnosis, avoidance of recurrent episodes of hypoglycemia and prompt management of hypoglycemia are the cornerstones of management to prevent brain damage and mental retardation in patients with CHI. Blood glucose levels must be maintained within the normal neonatal range (above 3.5 mmol/l), by administering glucose orally, enterally or intravenously. Usually, in neonates, the first step is a continuous enteral feeding of milk enriched with malto-dextrine. However, the severity of the hypoglycemias may straightaway or rapidly require more intensive treatments to prevent irreversible brain damages. The glucose rate administered has to be sufficient to normalize glucose levels, at least with a glucose flow equal to the physiological hepatic production of glucose (8–10 mg/kg/min for a neonate or young infant and 5–7 mg/kg/min for children). If hypoglycemia persists or recurs, the perfusion rate has to be increased, often requiring high concentration glucose solutions infused through a central venous line. However, in severe HI this may be insufficient and continuous glucagon infusion (intravenous or subcutaneous, 0.5 to 2 mg/day) along with glucose should be administered.

At the same time, specific treatments of HI must be initiated, which include diazoxide, octreotide and nifedipine.

### 7.1 Diazoxide

The clinical effectiveness of diazoxide is variable. Mutations in the *ABCC8/KCNJ11* gene are not predictive of the response to diazoxide, and there is no correlation between the histology and the clinical efficacy of diazoxide. Patients with transient and syndromic forms of HH will usually respond to diazoxide, whereas those with severe neonatal CHI will show no response. Oral diazoxide is first used at 15 mg/kg/day (neonates) or 10 mg/kg/day (infants) in oral doses. Diazoxide efficiency is defined as the normalization of glycemia >3 mmol/l measured before and after each meal in patients fed normally with a physiological overnight fast, after stopping intravenous glucose and any other medications for at least five consecutive days. The most frequent adverse effect is hypertrichosis, which can be marked and distressing in young children. Hematological side effects are very rare with usual administration doses. Two confirmed hypoglycemias (<3 mmol/l) in a 24-hour glucose measurement cycle defined the patient as diazoxide unresponsive. Dietary measures and glucose perfusion should be started again to maintain normoglycemia.

### 7.2 Octreotide

Octreotide is a long-acting analog of the natural hormone somatostatin and is used in the short- and long-term management of CHI. In the short term (with and without glucagon), it is used to stabilize patients pending further investigations. Octreotide has been successively used in the long-term management of some CHI patients in combination with frequent feeding. 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 be stressful on the family. A gastrostomy is recommended in these patients, as this will allow the delivery of bolus and continuous overnight feeds.

At initiation of octreotide treatment, some patients may present vomiting and/or diarrhea and abdominal distension, which will resolve spontaneously within 7–10 days. Gallbladder sludge or stones are rare but can necessitate ursodesoxycholic acid treatment. It should be

screened by abdominal ultrasound twice a year. Glycemia levels can rise significantly immediately after octreotide initiation, however this positive response can be transient, so that a 48 hour observation period should be performed to conclude definitively on the responsiveness to octreotide at a given dose.

### 7.3 Nifedipine

Other drugs as calcium channels blockers (like nifedipine, 0.5 – 2 mg/kg/day in 2 oral doses) can be proposed.

Patients who are resistant to medical treatment and require surgical treatment, must be assessed for their putative histological form of HI.

## 8. Differentiating focal from diffuse CHI

The gold standard method to determine which infants have fo-HI is intraoperative frozen section histology. This requires considerable histopathological expertise and will be most reliably performed in supraregional referral centres. Focal lesions are frequently not visible at laparotomy, although laparoscopic visualisation of the pancreas probably has an enhanced detection rate because of the magnification. It has been necessary to devise a number of strategies to differentiate fo-HI from di-HI preoperatively, as conventional imaging methods including ultrasound, octreotide scintigraphy, and magnetic resonance imaging are usually nondiscriminatory.

### 8.1 Invasive methods

Pancreatic venous sampling (PVS) has proven a valuable and reliable utility in differentiating foand di-HI and in localising focal lesions. The method relies upon transhepatic catheterization of the highly variable pancreatic venous anatomy and demonstration of persistent insulin secretion in the face of a low blood glucose concentration from one or more areas of the pancreas. The method requires that the infants medications are stopped for at least 48 h before the procedure, a specific method of general anaesthesia is administered and that blood glucose concentrations are kept <3.0 mmol/l throughout the procedure. Results may show generalised dysregulation of insulin secretion (di-HI), one or more hot spots of secretion (fo-HI), generalised suppression of secretion (focal disease with failure of catheterization of the region of the pancreas containing the lesion or an extrapancreatic source of insulin), or be uninformative (uninterpretable).

Where PVS has suggested the presence of fo-HI but not localised the lesion, and intra-arterial calcium stimulation test can be performed in which calcium is injected selectively into the gastroduodenal, superior mesenteric, and splenic arteries to stimulate insulin secretion. This method is good at localising focal disease but poor at confirming diffuse disease.

Some investigators have adopted a policy of early laparoscopic pancreatic biopsy. If no lesion is identified with the laparoscope, two or more biopsies from different regions of the pancreas are necessary.

### 8.2 Noninvasive methods

A variety of relatively noninvasive investigations including the i.v. tolbutamide test and the acute insulin response to an intravenous glucose load have been proposed to screen for fo-HI. The rationale for the tests depends either on the notion that, in fo-HI, the relatively quiescent pancreas outside the lesion can be further stimulated to secrete insulin.

Now 18fluoro-L-Dopa PET has been successfully used to localize the focal domain. The principle of this test is based on the fact that islets take up L-3,4-dihydroxyphenylalanine (L-dopa) and convert it to dopamine by dopa decarboxylase, present in the islet cells. However the precise role of dopamine in the pancreatic  $\beta$ -cells is currently unclear. 18fluoro-L-Dopa PET can also accurately locate ectopic focal lesions. 18fluoro-L-Dopa PET is highly sensitive in detecting focal lesions compared with the previous highly invasive techniques.

## 9. Surgical treatment

When medical and dietary therapies are ineffective, surgical treatment is required. If a focal lesion is identified and accurately located, it should be surgically removed, as this will “cure” the patient. As diffuse CHI is a heterogeneous disorder with respect to clinical presentation and response to medical therapy, the role of surgery in those cases that are diazoxide unresponsive is not so clear. Studies of predominantly Ashkenazi Jewish children with CHI suggest that the natural history of the disease is one of progressive glucose intolerance and clinical diabetes, possibly due to a slow progressive loss of  $\beta$ -cell function, and this may be due to the increased  $\beta$ -cell apoptosis, and, therefore, surgery may not be indicated in all patients. Similarly, some patients with diazoxide-responsive CHI go on to develop diabetes mellitus in adulthood.

Near-total pancreatectomy is a major operation and is associated with a high incidence of diabetes mellitus later in life. Clearly, surgery is indicated in those patients with severe diffuse disease who fail to respond to octreotide with frequent feeding regimens, and identification of this subgroup is important. The management of postpancreatectomy diabetes mellitus is complicated by the fact that these children have pancreatic exocrine insufficiency, glucagon deficiency, and have residual unregulated insulin secretion, and some patients show resistance to hyperketonaemia and diabetic ketoacidosis.

Before surgery, some precautions are necessary: i) stop medications several days before surgery (5 days before for diazoxide and 2 days before for octreotide) as they may interfere with the peroperative pathological analysis, ii) screen for gallbladder stones with an abdominal ultrasound, and treat if necessary and iii) supplement systematically with iron to prevent anemia.

## 10. Conclusion

CHI is a major cause of hypoglycaemia in the childhood period. Recognition and appropriate management of this type of hypoglycaemia are important to avoid long-term neurological consequences. The genetic mechanisms that lead to some forms of transient and CHI are beginning to be understood. Recent experience using 18 FL -dopa PET/CT scanning to distinguish diffuse from focal hyperinsulinism has completely changed the diagnostic and management approach to these patients. For the future, the management of medically unresponsive diffuse disease remains a challenge, and identifying the genetic mechanisms leading to both transient and persistent hyperinsulinism in the remaining 50% of the patients will provide novel insights into pancreatic  $\beta$ -cell physiology.

## 11. Acknowledgment

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## **Diabetes - Damages and Treatments**

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Over the last few decades the prevalence of diabetes has dramatically grown in most regions of the world. In 2010, 285 million people were diagnosed with diabetes and it is estimated that the number will increase to 438 million in 2030. Hypoglycemia is a disorder where the glucose serum concentration is usually low. The organism usually keeps the serum glucose concentration in a range of 70 to 110 mL/dL of blood. In hypoglycemia the glucose concentration normally remains lower than 50 mL/dL of blood. Hopefully, this book will be of help to many scientists, doctors, pharmacists, chemicals, and other experts in a variety of disciplines, both academic and industrial. In addition to supporting researcher and development, this book should be suitable for teaching.

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