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REVIEW ARTICLE

Congenital Hyperinsulinism: Overview and Clinical Update

Jan Marquard, Ertan Mayatepek, Thomas Meissner

Abstract:
Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycaemia in infancy. This review gives an overview and update of pathogenesis, genetics, diagnosis and management of CHI. This diesease is a genetically heterogeneous disorder with both familial and sporadic variants and is biochemically characterized by an unregulated secretion of insulin from pancreatic beta cells in relation to the blood glucose concentration. To date, there are eight different genes described which lead to CHI. However, in 50% of patients the genetic mechanism is still unknown. The clinical presentation is heterogeneous with regard to age of onset, severity and manner of symptoms. This is explained by different pathogenetic mechanism resulting in inappropriate insulin secretion. An early and rapid diagnosis including initiation of an effective treatment is essential for preventing hypoglycaemic brain damage and neurological sequelae in affected children. Over the last years, substantial progress in diagnostic with ^{18}F-L-dopa positron emission tomography for differentiating diffuse from focal disease and new laparoscopic surgery techniques has been made. In patients with diffuse form of CHI medical treatment with diazoxide, which is ineffective in patients with defects of the K_{ATP} channel, is the first line treatment. When medical treatment failed a near-total pancreatectomy has to be considered as a last resort. In patients with focal CHI a limited pancreatectomy can lead to complete cure of the disease. Patients should be managed by centres with a highly experienced team in diagnostic work-up and treatment of CHI.

Keywords: Congenital hyperinsulinism, hypoglycaemia, glucose
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Introduction and nomenclature

Hyperinsulinaemic hypoglycaemia (HH) is a collective term for a disease state caused by different reasons. These might be congenital (congenital hyperinsulinism), secondary to certain risk factors (such as maternal diabetes mellitus, intrauterine growth retardation, birth asphyxia and rhesus isoimmunisation) associated with developmental syndromes (such as Beckwith-Wiedemann, Costello and Kabuki) or due to other rare causes such as dumping syndrome, insulinoma, insulin gene receptor mutations or metabolic conditions as congenital disorders of glycosylation and tyrosinaemia type 1 [1]. Whereas transient forms of HH are typically seen in secondary causes (see above), congenital hyperinsulinism (CHI) [2] is usually persistent. CHI, previously called primary islet cell hypertrophy (nesidioblastosis), familial hyperinsulinism or persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), is the most common cause of persistent hypoglycaemia in infancy [3]. CHI is a genetically heterogeneous disorder with both familial and sporadic variants. It is biochemically characterized by an unregulated secretion of insulin from pancreatic beta cells in relation to the blood glucose concentration. The severity of the disease varies from life-threatening hypoglycaemia in neonates within the first days of life which may require

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a near total pancreatectomy and mildly symptomatic hypoglycaemia with initial manifestation in adolescence or adulthood that may be difficult to identify [4,5]. Affected children are at high risk for brain damage and subsequent neurodevelopment handicap through prolonged and/or recurrent hypoglycaemia [6], so diagnosis and prompt treatment are essential to avoid damage from the developing brain.

Definition CHI

CHI is a group of disorders characterized by:

- Dysregulated secretion of insulin from pancreatic beta cells in relation to blood glucose concentration.
- Recurrent or persistent hypoglycaemia.
- Underlying genetic aetiology.

Epidemiology

The incidence of CHI in the northern European population is about 1:30.000-50.000 live births [7], the majority of cases has been described as sporadic [8]. The incidence is raised in populations with a founder effect (e.g. 1:3200 in central Finland [9]) or populations with high prevalence of consanguinity (e.g. 1:2675 in Saudi Arabia [10]).

Pathogenesis and Genetics

Under normal physiological condition in fasting states only a small amount of insulin is secreted and blood glucose levels are regulated within normal ranges (3.5-5.5 mmol/l). In children suffering from CHI insulin secretion from pancreatic beta cells is dysregulated in terms of increased insulin secretion in relation to a low blood glucose concentration. Causally there is an abnormal function of the ATP-dependent potassium (K_{ATP}) channel, disturbances of enzymes due to mutations affecting the ATP/ADP-ratio and thereby lowering the threshold for glucose-stimulated insulin secretion or mutations leading to accumulation of intermediary metabolities, triggering insulin secretion in beta cells. Some authors classify defects of the K_{ATP}-channels into "channelopathies" and defects with increased beta cell ATP/ADP ratio or defects leading to accumulation of intermediary metabolites into "metabolopathies" [11]. Knowledge about the underlying gene mutation which causes hyperinsulinism is essential for management and prognosis. Figure 1 summarizes the pathophysiology, Table 1 shows the to date known gene mutations in pancreatic beta cells causing CHI.

In approximately 50% of CHI-cases in none of the yet known gene a mutation is found, suggesting the existence of other disease-associated genes [12].

In addition, CHI can be classified by histological findings into a diffuse, focal and atypical form [13,14]. Diffuse CHI is inherited in an autosomal recessive or dominat manner, usually due to recessive mutations in genes encoding the K_{ATP}-channel and is characterized by an increase in the size of pancreatic beta cell nuclei throughout the whole of the pancreas. Focal CHI is sporadic in inheritance and is due to a focal loss of the maternal allele from chromosome 11p15 in combination with a paternally inherited K_{ATP} channel mutation [15]. Enlargement of the beta cell nuclei is thereby confined to the focal lesion. The atypical form of CHI is seen rarely and is due to mosaic interstitial paternal uniparental isodisomy in patients with dominantly inherited gene mutations in the K_{ATP}-channel with the coexistence of normal and abnormal islets [14].

The most common form of CHI is due to defects of the K_{ATP}-channel which plays an essential role in regulation of insulin secretion from the pancreatic beta cell by transforming metabolic signals to electrical changes in membrane potential (Figure1). Defects in the K_{ATP} channel results in closure of potassium channels, depolarization of the beta cell membrane, calcium ions influx and following insulin secretion despite the presence of hypoglycaemia. The pancreatic K_{ATP}-channel is a functional complex of sulfonylurea receptor 1 (SUR1) composed of four regulatory subunits and the inwardly rectifying potassium channel subunit, Kir6.2 that surrounds a central pore. SUR1 can be activated by diazoxide and Mg-ATP and inhibited by sulfonylureas, Kir6.2 can be activated by fatty acid metabolities. Usually the mutations in the genes *ABCC8* and *KCNJ11* (encoding the two subunits SUR1 and Kir6.2) are autosomal recessively inherited [16,17], however autosomal dominant mutations have also been described [18]. Beside structural defects in the K_{ATP} channel itself also failures in regulation of the channel are known [19].

As reported above, a focal loss of the maternal allele from chromosome 11p15 in combination with a paternally inherited K_{ATP}-channel mutation leads to focal beta cell hyperplasia and hyperinsulinaemia in the affected focal lesion (loss of heterozygosity). Several imprinted genes are located within the chromosomal region 11p15. Beside the genes encoding the K_{ATP}-channel there are also genes located encoding tumor suppressor genes. Therefore, beta cell hyperplasia can be explained by loss of expression of maternally tumor suppressor genes [20]. However, for dysregulated insulin secretion a paternally inherited mutation in the K_{ATP}-channel is required. Focal adenomatous hyperplasia of islet cells of the pancreas is detected in approximately 30-40% of sporadic cases in which pancreatectomy is performed [15, 21].

Gain of function mutations in the *GLUD1* gene, encoding the enzyme glutamate dehydrogenase (GDH), are the second common cause [22] of CHI resulting in the hyperinsulinism/hyperammonaemia (HI / HA) syndrome [23]. The familial form is dominantly inherited.

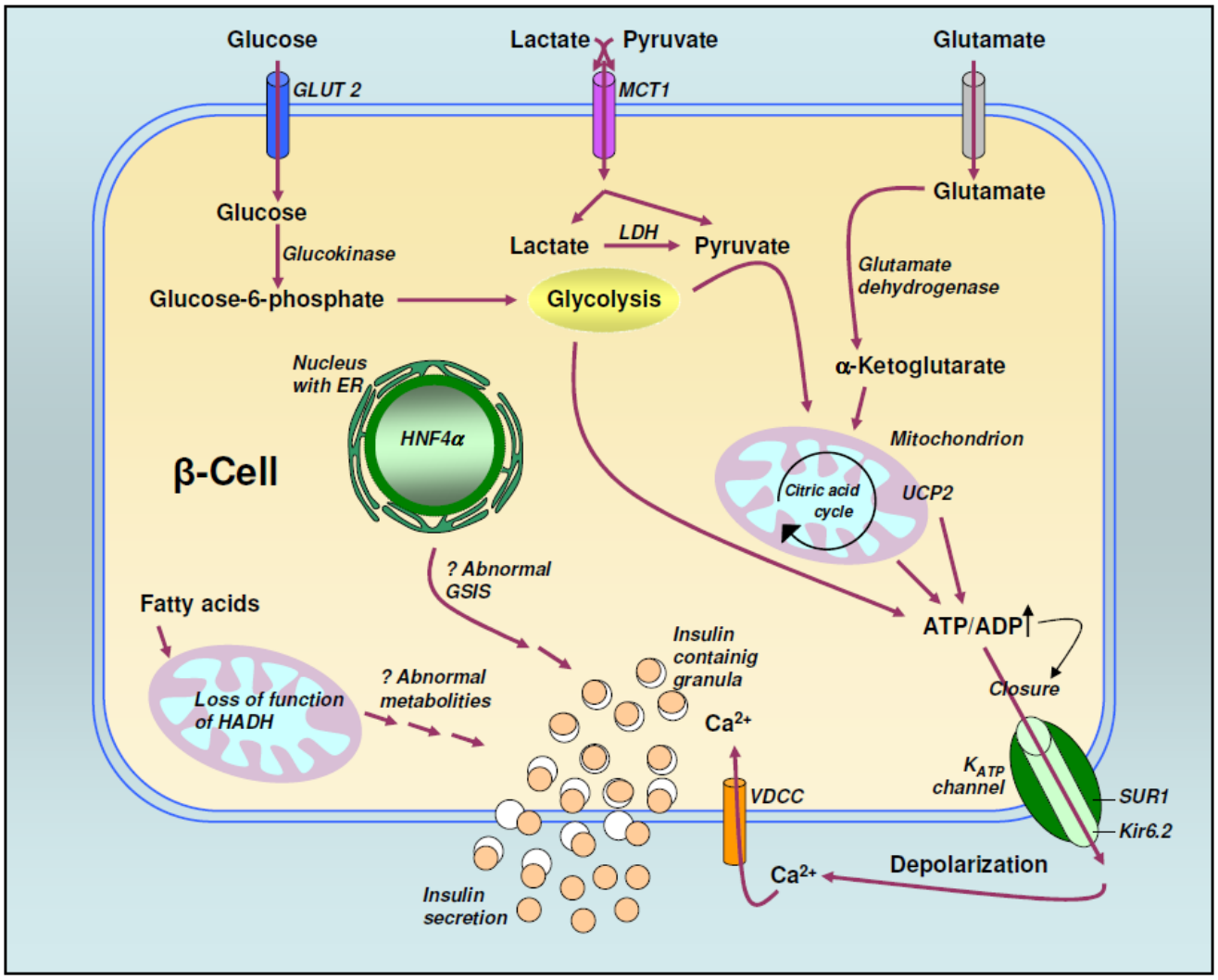

Figure 1. Simplified model of pancreatic beta cell and the proteins implicated in congenital hyperinsulinims (CHI).

Glucose is transported into the beta cell by glucose-transporter protein 2 (GLUT-2) on the cell surface. The CHI-associated glycolytic enzyme glucokinase phosphorylates glucose to glucose-6-phosphate and functions as the glucose sensor and is the rate-limiting step in glucose metabolism. Degradation of glucose increase the ATP/ADP-ratio which is sensed by the ATP-sensitive potassium (K_{ATP}) channels. A high ATP/ADP ratio by glycolysis and citric acid cycle leads to inhibition and closure of the K_{ATP} channels, following by depolarization of the plasma membrane and opening of the voltage-dependent calcium channels (VDCC). Thus, results in an influx of extracellular calcium which is the triggering signal for fusion of insulin containing granula with the plasma membrane and finally exocytosis of insulin. An „activating“ mutation in the gene encoding glucokinase leads to overacting of beta cell glucokinase activity, leading to increased glucose posphorylation, lowering the threshold for glucose-stimulated insulin secretion (GSIS) and finally raising the ATP/ADP ratio. An „activating“ mutation in the gene encoding glutamate dehydrogenease (GDH) results in an increased activity of GHD. Increased α-ketogluterate levels serve as substrate for the citric acid cylce leading to an increased ratio of ATP/ADP. Dominant mutations in the gene encoding moncarboxylate transporter 1 (MCT1) causing exercise induced CHI by increased expression of MCT1 in beta cells where this gene is not usually transcribed. Thereby the beta cell becomes oversensitive to acute changes (by physical exercise) in the extracellular concentrations of lactate and pyruvate, resulting in pyruvate uptake and thereby raising the ATP/ADP-ratio. The mitochondrial uncoupling protein 2 (UCP2) induces uncoupling of mitochondrial oxidative metabolism from ATP synthesis resulting in reduction of ATP yield from substrate oxidation. Loss-of-function mutations encoding UCP2 lead to increased ATP synthesis and enhanced GSIS. Loss-of-function mutations encoding the two subunits SUR1 and Kir6.2 of the pancreatic K_{ATP} channel are the most common genetic causes of CHI. Outflow of potassium is increased or stopped leading to persistent depolarization of the beta cell membrane. The molecular mechanisms leading to CHI in gene mutations encoding 3-hydroxyl-CoA dehydrogenase (HADH) and hepatocyte nuclear factor 4 alpha (HNF4α) are unclear to date. LDH, Lactate dehydrogenase. ER, endoplasmic reticulum.

Table 1 Current classification and different genes involved in pathogenesis of CHI

Disease	Gene	Protein	OMIM	Characteristics
K_{ATP}-HI diffuse	*ABCC8 KCNJ11*	Sulfonylurea receptor 1 (SUR1)/ Inward rectifiying potassium channel (Kir6.2)	600509 600937	Most common form; severe neonatal type of CHI; no response to diazoxide
K_{ATP}-HI focal	*ABCC8/ KCNJ11 loss of hetero-zygousus*			Focal loss of the maternal allele from chromosome 11p15 and paternally germline mutation; complete cure with limited pancreatectomy
GDH-HI	*GLUD1*	Glutamate dehydrogenase (GDH)	138130	Mostly mild hyperammonaemia, good response to diazoxide
GCK-HI	*GCK*	Glucokinase	138079	Heterogenous; diagnostic difficulties; postprandial hypoglycaemia
EI-HI	*SLC16A1*	Monocarboxylate transporter 1 (MCT1)	600682	Hypogycaemia after physical exercise
HADH-HI	*HADH*	3-hydroxylacyl-CoA dehydrogenase (HADH)	601609	Increased 3-hydroxybutyryl-carnitine
HNF4A-HI	*HNF4A*	Hepatocyte nuclear factor 4 alpha	600281	Most frequently transient hyperinsulinism but persistent hyperinsulinism is also reported; macrosomia at birth
UCP2-HI	*UCP2*	Uncoupling protein 2	601693	Recently described; few cases

GDH is a mitochondrial matrix enzyme located in pancreas, kidney, brain and liver and catalyzes the conversion of glutamate to α-ketogluterate and ammonia. Usually, GDH is allosterically inhibited by GTP and activated by leucine [24], gene mutations in *GLUD1* lead to loss of ihibition by GTP resulting in increased enzyme activity. This explains the typically protein induced (leucine sensitivity) hyperinsulinaemic hypoglyceamia in these patients, but also fasting hypogylceamia occurs. In the beta cell α-ketogluterate enters the citric cycle and leads to increases of the ATP/ADP-ratio, closure of K_{ATP}-channels, depolarization of beta cell membrane and finally insulin secretion. In liver cells the activating mutations lead to asymptomatic, persistent elevations of plasma ammonium levels.

Glucokinase hyperinsulinism is a rare variant of CHI caused by activating mutations in the glucokinase gene (*GCK*) resulting in overactivity of glucokinase within the pancreatic beta cell [25]. The glycolytic enzyme glucokinase functions as the "glucose sensor" in the pancreatic beta cells and as such regulates glucose stimulated insulin secretion (GSIS) [26]. Gain of function mutations of *GCK* are autosomal dominantly inherited and lower the threshold for GSIS leading to dysregulated insulin secretion in relation to already low blood glucose concentrations. To date, there are only twelve activating G*CK* mutations described found in eight families andseven individuals [27-29]. Heterozygous inactivating mutations in *GCK* result in a type of monogenic diabetes known as maturity onset diabetes of the young 2 (MODY2) [30], and homozygous inactivating mutations lead to permanent neonatal diabetes [31].

An increased expression of monocarboxylate transporter 1 (MCT1) in pancreatic beta cells due to mutations in the *SLC16A1* gene cause exercise-induced hyperinsulinism (EIHI) [32]. EIHI is dominantly inherited and characterized by inappropriate insulin secretion during anaerobic exercise or on pyruvate load [33-35]. By over expression of MCT1 (which is usually not expressed in beta cells) the beta cell becomes oversensitive to acute changes (by physical exercise) in the extracellular concentrations of lactate and pyruvate, resultuing in increased pyruvate uptake and thereby raising the ATP/ADP-ratio. So far, 13 patients are diagnosed, 12 of two families and one unrelated patient.

3-hydroxyacyl CoA dehydrogenase (HADH, formerly SCHAD) deficiency is a rare cause of CHI, only 5 patients are reported to date [36,37]. HADH, encodes by the *HADH* gene, catalyzes the penultimate reaction in the mitochondrial fatty acid oxidation spiral, the NAD+-dependent conversion of 3-hydroxyacyl-CoA to 3-ketoacyl-CoA [38]. Loss-of-function mutations in the *HADH* gene are autosomal recessively inherited and

associated with CHI but the mechanism which leads to dysregulated insulin secretion is not known at present. It is assumed that HADH deficiency can cause disturbance of the ATP/ADP-ratio in the pancreatic beta cell. Usually plasma acylcarnitine profiles in affected patients show strongly increased 3-hydroxybutyryl-carnitine and normal C2-carnitine levels [39].

Heterozygous mutations in the transcription factor hepatocyte nuclear factor (HNF)-4α (encoded by the *HNF4A* gene) are associated with MODY1 and transient or persistent CHI [40,41]. The mutations are also associated with macrosomia at birth [42]. The mechanism by which HNF4A mutations lead to CHI is unclear to date and the finding of transient or persistent CHI is unexpected, since heterozygous mutations in the *HNF4A* gene lead to MODY1 with loss of glucose-induced insulin secretion and glucose intolerance in these patients.

Recently, a further gene in which mutations are suspected leading to CHI has been described. The mitochondrial uncoupling protein 2 (UCP2), encoded by the *UCP2* gene, induces uncoupling of mitochondrial oxidative metabolism from ATP synthesis resulting in reduction of ATP yield from substrate oxidation in the pancreatic beta cell [43]. Loss-of-function mutations encoding UCP2 lead to increased ATP synthesis and enhanced GSIS. UCP2 knockout mice exhibit hyperinsulinaemic hypoglycaemia. In two children with CHI, UCP2 variants encoding amino-acid changes were found, functional assays showed an impaired activity of these UCP2 mutants [44].

Clinical Presentation

Clinical presentation of CHI is heterogenous with regard to age of onset, severity as well as manner of symptoms and sequelae. In a review of 114 patients with CHI, 65 % became manifested as neonates, 28 % as infants and 7% during childhood [45]. Symptoms depending mainly on age of onset. Neonates with CHI usually present with severe neuroglycopenic symptoms like seizures and coma (>50%), however, non-specific signs like cyanosis, poor feeding and irritability and asymptomatic hypoglycaeamia (20%) also occur [45]. Affected neonates typically show very short fasting tolerance and normoglycaemia can only be achied by continious intravenous glucose infusion. Approximatley one-third of neonates are macrosomic [45], which reflects the exposure to intrauterine hyperinsulinaemia, particulary macrosomia is seen in newborns with HNF4A-HI. Hypertrophic cardiomyopathy and hepatomegaly which is commonly seen in newborns with CHI is also due to fetal hyperinsulinaemia [46]. In general, neonatal onset of CHI is most often caused by diffuse or focal K_{ATP}-HI.

Children advanced in years rather show symptoms of hypoglycaemia associated with activation of the autonomic nervous system and epinephrine release like weakness, hunger, nausea and anxiety.

The clinical variability and age of onset of individuals with mutations in *GLUD1* gene and *GCK* gene is broad. Clinical manifestions of patients with HI/HA syndrome (GDH-HI) include post-prandial hypoglycaemia following protein meals, as well as fasting hypoglycaemia, diet-independent hyperammonaemia and seizures indepent of hypoglycaemia [47-49]. In a small study in 14 patients with HI/HA syndrome, the median age at onset of hypoglycaemia was 9 months [50]. In GCK-HI clinical presentation varies between severe hypogylcaemia in the newborn and adults with only mild or no symptoms of hypoglycaemia in long fasting states. In the late-onset form of GCK-HI hypoglycaemic episodes are usually less severe and less frequent, making a correct diagnosis difficult [27].

As reported above, patients with EIHI show hypoglycaemia typically during and particularly immediately after exercise [32].

Diagnosis

An early and rapid diagnosis including initiation of an effective treatment is essential for preventing hypoglycaemic brain damage and neurological sequelae. The most important and powerful diagnostic criterion in neonates is the glucose infusion rate required to maintain normoglycaemia. An increased intraveneous glucose requirement of >8-10 mg/kg/minute is nearly diagnostic for CHI, but also for transient HH [11]. In HH a characteristically pattern of laboratory findings could be observed and diagnosis is usually easily established. At the time of hypoglycaemia (blood glucose <2.0 mmol/l) plasma insulin concentration is inappropriately elevated (>3 mU/l). Even if insulin concentrations range between normal levels it has to be considered that it is abnormal in the context of a low blood glucose concentration and that there is no correlation between serum insulin and glucose levels. Thereby the term "hyperinsulinism" can be misleading because very high serum insulin levels are rarely found. As a consequence of the inappropriate insulin secretion, lipolysis is intermitted resulting in low concentrations of free fatty acids (<600 µmol/l) and serum ketone bodies (beta-hydroxybutyrate usually <0.1 mmol/l). Usually ketonuria could also be observed but the absent from ketone bodies from the urine does not exclude CHI [51]. Further findings include elevated concentration of C-peptide (>0.2 nmol/l) and proinsulin (>5 pmol/l) as well as inappropriate low serum cortisol and glucagon levels due to a blunted counterregulatory hormonal response [52,53].

The glycaemic response, defined as an increase in blood glucose levels of more than 30% of the basis glucose value after glucagon injection (100 µg/kg i.m. or s.c., max 1mg),

Table 2 Typical laboratory findings in CHI	
Laboratory value	**Finding**
in state of hypoglycaemia (blood glucose <2 mmol/l)	
Serum insulin	**increased (>3 mU/l)**
Serum C-peptid	**increased (>0.2 nmol/l)**
Serum proinsulin	**increased (>5 pmol/l)**
Serum ketone bodies (beta-hydroxybutyrate)	**low (<0.1 mmol/l)**
Serum free fatty acids	**low (<600 µmol/l)**
Serum IGFBP-1	**decreased**
in HI/HA syndrome (GDH-HI)	
Serum ammonia	**increased (up to 200 µmol/l)**
in HADH deficiency (HADH-HI)	
Plasma 3-hydroxybutyryl-carnitine (acylcarnitine profile)	**increased**

indicate mediation of the hypoglycaemia by insulin [54]. Also low serum levels of IGFBP-1 at the time of hypoglycaemia provide an additional marker of CHI in pediatric patients [55].

Elevated serum ammonia levels (up to 200 µmol/l] are pathognomonic for the HI/HA syndrome, so measurement of ammonia should always be performed in each patient with CHI, but normal ammonia concentrations do not exclude GDH-HI [56]. In patients with HADH-HI, usually plasma acylcarnitine profiles show strongly increased 3-hydroxybutyryl-carnitine and normal C2-carnitine levels. The feasible laboratory findings in CHI are summarised in Table 2.

In neonates with CHI hypoglycaemia usually occurs in response to short-term fasting within one or two hours after feeding. However, in cases with first manifestation of CHI after 10 days of life, especially in patients with initial manifestation in adolescence or adulthood, diagnosis could be difficult and will optionally require provocation testing. In GDH-HI hypoglycaemia may occur after eating a leucin- or protein-rich meal. A standardised leucine tolerance test (50mg/kg p.o. or 15 mg/kg i.v.) leads to an increase in plasma insulin in some affected patients but may also lead to life-threatening hypoglycaemia. So, today the molecular genetic exploration of mutations in the *GLUD1* gene is preferred. Diagnosis of GCK-HI could be very complex because of a huge clinical variability of the disease. In some cases of GCK-HI postprandial hypoglycaemia was observed but not obligatory present [27]. Hypoglycaemia in connection with physical exercise may indicate EIHI. Affected patients become hypoglycaemic within 30 minutes after a short period of anaerobic exercise. An exercise test with sub-maximal to maximal exercise (heart rate: 220 – age) over 10 minutes can be performed, insulin, glucose and lactate levels should be measured at point of time: -10, 0, 5, 10, 15, 20, 25, 30, 40 50, 60 minutes. In patients with late onset of CHI the genetic analysis should be requested on the basis of clinical and optionally other laboratory findings.

When diagnosis of CHI is established in a newborn by laboratory and clinical findings the following diagnostic steps are depending on the response to diazoxide. An early molecular genetic analysis for the known mutations, especially for K_{ATP} channelopathies, could be helpful but is not mandatory. The drug diazoxide opens the K_{ATP} channel by binding to the intact SUR1 component, hence diazoxide is often ineffective in CHI due to channelopathies but effectice in virtually all forms of HH.
In patients who are "diazoxide responsive" no further immediate diagnostic procedures have to be done, molecular genetic analysis should be performed on the basis of the phenotype and may have impact for follow up. "Diazoxide unresponsive" individuals are highly suspected to have a mutation in the *ABCC8* or *KCNJ11* gene, encoding the K_{ATP} channel, a rapid genetic analysis of this genes should be performed. The question arises whether the patient has a focal or a diffuse form of the disease

because further management is radically different. Patients who are homozygous or compound heterozygous for *ABCC8* or *KCNJ11* (or gene mutation encoding "metabolopathies") have a diffuse form and need no further examination (excepting follow up). If a paternal mutation in *ABCC8* or *KCNJ11* is detected (or no mutations in these genes) a focal disease might be present and further imaging studies with ^{18F}DOPA-PET/CT (Fluorine-18 L3,4-dihydroxyphenylalanine positron emission tomography) scan to distinguish focal from diffuse form and for precise preoperative localisation of the focal lesion are required [1]. The principle of the ^{18F}DOPA-PET/CT scan is the fact that beta cells have the ability to take up L-DOPA and convert it into dopamine. This step is correlated with the activity of the aromatic amino acid decarboxylase and is increased in the hyperfunctional affected pancreatic area in comparison to normally functioning pancreas [57]. In comparison to histological data ^{18F}DOPA-PET/CT has a sensitivity of about 94-96% and a specificity of 100% [58,59]. In the last years PET/CT has displaced highly invasive localisation methods such as intrahepatic pancreatic portal venous sampling or the intra-arterial calcium stimulation/venous sampling test. Further imaging assessment of the pancreas with ultrasonography, CT or MRI are not informative in CHI.

Differential Diagnosis

CHI is the most common cause of HH in infancy [3] but in neonates with HH there exist several potential differential diagnoses. "Secondary" causes of HH are usually transient and due to maternal diabetes mellitus (gestational and insulin dependent) [60], intrauterine growth retardation [61], birth asphyxia [62] and rhesus isoimmunisation [63]. A spontaneous resolution of transient hyperinsulinism was observed at a median age of 181 days (range 18 to 403 days) in a study with 26 infants who had HH for months, which then spontaneously resolved [64].

Hyperinsulinism may be also present in patients with a syndromal phenotype. In patients with Beckwith-Wiedemann syndrome, HH occurs in about 50% [65] beside macroglossia, pre or postnatal growth >90th percentile, abdominal wall defects, ear creases or pits, facial naevus flammeus and renal abnormalities. Hyperinsulinism in BWS is reported as transient and prolonged [66]. Further known rare syndromal diseases related to HH are Sotos [67], Kabuki [68], Usher [69], Costello [70], Timothy [71], Trisomy 13 [72], Mosaic Turner [73] and central hypoventilation syndrome [74]. Metabolic conditions may also lead to HH, such as congenital disorders of glycolysation [75] and tyrosinaemia type 1 [76]. HH due to insulinoma (sporadic or associated with multiple endocrine neoplasia type 1) is very rarely seen in children [77]. In one family with autosomal dominant HH a mutation in the human insulin receptor gene is suspected to cause the disease [78]. Factitious hyperinsulinism due to Munchausen syndrome by proxy has been also reported in literature [79].

Management

Medical management

The primary goal of treatment is to prevent neurologic symptoms and sequelae by maintaining normoglyceamia (blood glucose >3.0 mmol/l).

Initial medical treatment: In neonates with HH initial medical treatment is an adequate carbohydrate substitution with intravenous glucose at high concentrations and additional feeding via a nasogastric tube with glucose polymers. In neonates with high glucose requirements a central venous catheter or an umbilical venous catheter may be necessary for high concentrated glucose infusion (> glucose 10%). In severely affected neonatal patients additional continuous intravenous infusion of glucagon has been shown to be most effective in maintaining normoglycaemia and reducing glucose requirement but there is no benefit for long-term treatment [80]. Additionally intravenous somatostatin treatment or application of the somatostatin analogue octreotide may also be helpful in reducing glucose requirements but side affects have to be considered (Table 3).

Long-term treatment: The first-line medication for long term treatment is diazoxide which can be administered orally, however clinical effectiveness and response is variable [81]. In patients with *ABCC8* or *KCNJ11* gene mutations diazoxide is effectless, also 90% of neonates do not respond to diazoxide. The initial dose is 5-7.5 mg/kg per day divided into three doses. The dosage could be increased every two days at 5 mg to the effective and tolerated dose (max. 15 mg/kg/day). In patients who do not respond to diazoxide 15 mg/kg per day, increasing the dose will only increase the risk and severity of side effects, a benefit could not be expected. The most common side effects of diazoxide are fluid retention, hypertrichosis, hyperuricaemia, tachycardia, leucopenia and feeding problems. Additionally, the thiazide diuretic hydrochlorothiazide (2-10 mg/kg per day divided into 2 doses) can be given to reduce water retention and further reduction of insulin secretion. If dose of diazoxide falls below 5 mg/kg per day a trial off diazoxide should be considered under medical observation in hospital. Octreotide is a long acting somatostatin anlogue and acts mainly by inhibition of insulin secretion by activation of somstostatin receptor-5 and inhibition of calcium mobilisation in the beta cell. It can serve as second line treatment in diazoxide unresponsive patients [82].

Table 3 Drug treatment - Initial stabilisation of blood glucose in neonatal manifestation

Medication	Dose	Characteristics
Glucose	10-20 mg/kg/min i.v.	Sole substitution of glucose with peripheral i.v. access is usually impossible for maintaining normoglycaemia. Additional carbohydrates p.o. or central i.v. access for highly concentrated glucose infusion
Glucagon	1-20 µg/kg/h i.v.	Continious i.v.; in case of no i.v. access as bolus s.c., for emergency treatment of hypoglycaemia 0.5-1 mg i.m.
Octreotide	5-30 µg/kg/day s.c.	Continuous s.c. infusion or divided in 4-6 single doses

i.v. intravenous; s.c. subcutaneous; i.m. intramuscular; p.o. orally administered

Table 4 Drug treatment – Long-term management

Medication	Dose	Characteristics
Diazoxide	5-15 mg/kg/day p.o. divided into 3 doses	Common side effects: fluid retention, hypertrichosis, frequently no response to diazoxide, trial of treatment over at least 5 days
Chlorothiazide (used in conjunction with diazoxide)	2-10 mg/kg/day p.o. divided into 2 doses	If daily dose of diazoxide is >10mg/kg, could prevent fluid retention, synergistic response with diazoxide, monitor serum electrolytes
Octreotide	5-20 (30) µg/kg/d s.c.	Continuous s.c. infusion or divided in 4-6 single doses
Nifedipine	0.25-2.5 mg/kg/day p.o. divided into 3-6 doses	Limited experience, usually ineffective as mono treatment

s.c. subcutaneous; i.m. intramuscular; p.o. orally administered

Octreotide (5-20 µg/kg/d) is given subcutaneously 4-6 times daily or continuous via medication pump. In some patients octreotide may also be a long-term treatment option in combination with frequent feeding in place of pancreatectomy [83]. Side effects are amongst others anorexia, nausea, abdominal pain and suppression of growth hormone, TSH and ACTH, so linear growth should be observed closely in these patients. Another starting point reducing insulin secretion is to block the voltage-dependent calcium channels with calcium-channel blockers (eg, nifedipine). There are some case reports about reducing insulin secretion or reducing the doses of other agents by nifedipine in patients with CHI [84-86] but the therapeutic efficacy of calcium-channels remains unclear.

However, a mono treatment with nifedipine in patients with severe CHI is no option. A summary of the medications used in the long-term management of CHI is drafted in Table 4.

Surgical Management

In patients with focal CHI a limited pancreatectomy can lead to complete cure of the disease. Laparoscopic enucleation of a focal lesion is recommended and should be the first line approach because of less peri- and postoperative complication in comparison with the open approach [87,88]. When medical treatment in severe cases of diffuse CHI has failed and discharge to home with medical treatment in addition with nutritional management

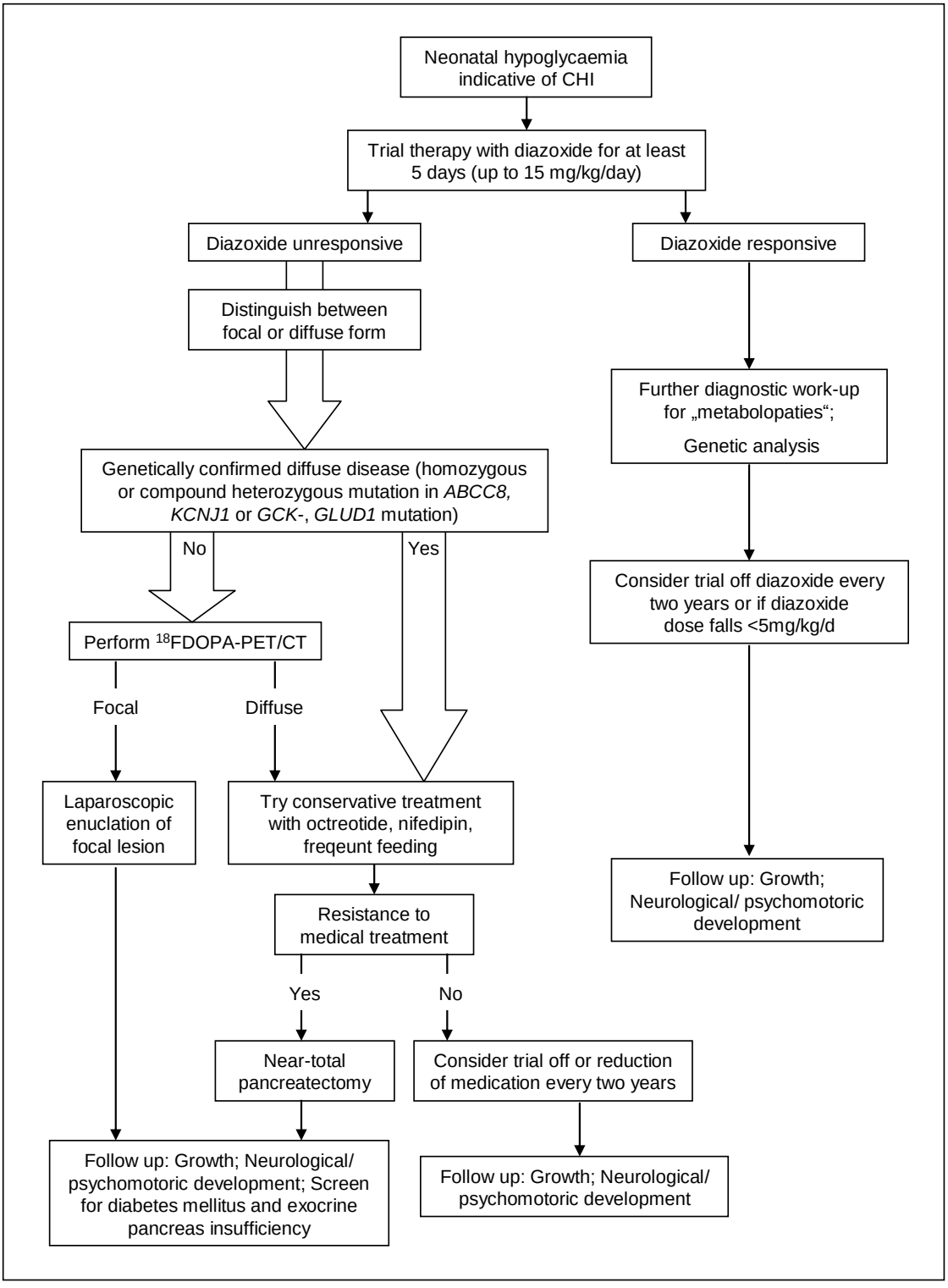

Figure 2. Flow chart for a proposed diagnosis, management and follow up of neonates with CHI.

is not possible, a near-total pancreatectomy (95-97%) has to be considered as last resort [89]. Near-total pancreatectomy carries a high risk for the future developing diabetes mellitus and pancreatic exocrine insufficiency [90], hence, near-total pancreatectomy is reserved for patients with diffuse disease and resistance to medical treatment.

Complications and Follow up

Neurologic sequelae such as psychomotor retardation, cognitive deficits and epilepsy are usually due to prolonged and/or recurrent hypoglycaemia in the newborn period. A long-term follow-up of 114 patients with congenital hyperinsulinism showed that the general outcome was poor with a high degree of psychomotor or mental retardation (44%) or epilepsy (25%) [45]. In another trospective study of 90 patients with CHI, 21% of patients had severe or psychomotor retardation and 16 % had epilepsy [6]. Both studies showed that the neurologic sequelae were more common among patients diagnosed as neonates.

Beside regular monitoring of development and growth, follow-up of patients should focus on psychomotor and neurologic development (e.g. EEG, psychometric testing, evaluation of school carrier). For patients who undergo surgery glucose tolerance (HBA_{1c}, oral glucose tolerance test) and exocrine pancreas function (pancreas-specific elastase in faeces) should be monitored regularly. In patients with diazoxide or octreotide treatment a trial off should be considered every two years under medical observation in hospital, especially, if glucose levels are always within the normal range without hypoglycaemia or in case of low doses required for maintaining normoglycaemia because some patients can enter spontaneous remission.

The flow chart demonstrated in Figure 2 is outlining the proposed diagnosis, management and follow up of neonates with CHI.

Conclusion

During the last years new insights in the pathophysiology and genetics of CHI were found but to date in up to 50% of patients the genetic mechanism is still unknown. The diagnostic and management approach has completely changed by recent advances in imaging techniques (^{18F}DOPA-PET/CT) and laparoscopic surgery. CHI remains a rare heterogeneous disorder with different responses to treatment. After diagnosis of HH a prompt treatment is essential, to avoid further damage from the developing brain. Further diagnosis and management should be performed in centres with a highly experienced team in diagnostic work-up and treatment of this disease.

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