Current opinion in pediatric metabolic disease

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Congenital Hyperinsulinism: Overview and Clinical Update

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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
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<sub>ATP</sub>) 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 metabolites, triggering insulin secretion in beta cells. Some authors classify defects of the K<sub>ATP</sub>-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<sub>ATP</sub>-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<sub>ATP</sub> 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<sub>ATP</sub>-channel with the coexistence of normal and abnormal islets [14].

The most common form of CHI is due to defects of the K<sub>ATP</sub>-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<sub>ATP</sub> 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<sub>ATP</sub>-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 metabolites. 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<sub>ATP</sub> 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<sub>ATP</sub> 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<sub>ATP</sub>-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<sub>ATP</sub>-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.
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\textsubscript{ATP}) channels. A high ATP/ADP ratio by glycolysis and citric acid cycle leads to inhibition and closure of the K\textsubscript{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 phosphorylation, lowering the threshold for glucose-stimulated insulin secretion (GSIS) and finally raising the ATP/ADP ratio. An “activating” mutation in the gene encoding glutamate dehydrogenase (GDH) results in an increased activity of GDH. Increased α-ketogluterate levels serve as substrate for the citric acid cycele leading to an increased ratio of ATP/ADP. Dominant mutations in the gene encoding monocarboxylate transporter 1 (MCT1) causes 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\textsubscript{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.
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 GCK mutations described found in eight families and seven 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, resulting 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 enocding UCP2 lead to increased ATP synthesis and enhanced GSIS. UCP2 knockout mice exhibit hyperinsulinemic 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 hypoglycaemia (20%) also occur [45]. Affected neonates typically show very short fasting tolerance and normoglycaemia can only be achieved by continuous intravenous glucose infusion. Approximately one-third of neonates are macrosomic [45], which reflects the exposure to intrauterine hyperinsulinaemia, particular 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<sub>ATP</sub>-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 manifestations 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 hypoglycaemia 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 intravenous 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 interrupted 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 1 mg),
Table 2  Typical laboratory findings in CHI

<table>
<thead>
<tr>
<th>Laboratory value</th>
<th>Finding</th>
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<tbody>
<tr>
<td><strong>in state of hypoglycaemia (blood glucose &lt;2 mmol/l)</strong></td>
<td></td>
</tr>
<tr>
<td>Serum insulin                                                                    increased (&gt;3 mU/l)</td>
<td></td>
</tr>
<tr>
<td>Serum C-peptid                                                                   increased (&gt;0.2 nmol/l)</td>
<td></td>
</tr>
<tr>
<td>Serum proinsulin                                                                 increased (&gt;5 pmol/l)</td>
<td></td>
</tr>
<tr>
<td>Serum ketone bodies (beta-hydroxybutyrate)                                      low (&lt;0.1 mmol/l)</td>
<td></td>
</tr>
<tr>
<td>Serum free fatty acids                                                           low (&lt;600 µmol/l)</td>
<td></td>
</tr>
<tr>
<td>Serum IGFBP-1                                                                    decreased</td>
<td></td>
</tr>
<tr>
<td><strong>in HI/HA syndrome (GDH-HI)</strong></td>
<td></td>
</tr>
<tr>
<td>Serum ammonia                                                                    increased (up to 200 µmol/l)</td>
<td></td>
</tr>
<tr>
<td><strong>in HADH deficiency (HADH-HI)</strong></td>
<td></td>
</tr>
<tr>
<td>Plasma 3-hydroxybutyryl-carnitine (acylcarnitine profile)                         increased</td>
<td></td>
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</tbody>
</table>

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 leucine- 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 effective 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 \textit{ABCC8} or \textit{KCNJ11} (or gene mutation encoding “metabolopathies”) have a diffuse form and need no further examination (excepting follow up). If a paternal mutation in \textit{ABCC8} or \textit{KCNJ11} is detected (or no mutations in these genes) a focal disease might be present and further imaging studies with\textsuperscript{18}F-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\textsuperscript{18}F-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 \textsuperscript{18}F-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 naeves 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 glycolysis [75] and tyrosinaemia type I [76]. HH due to insulinoma (sporadic or associated with multiple endocrine neoplasia type I) 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 normoglycaemia (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 effects 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 \textit{ABCC8} or \textit{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 anologue and acts mainly by inhibition of insulin secretion by activation of somatostatin 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>10-20 mg/kg/min i.v.</td>
<td>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</td>
</tr>
<tr>
<td>Glucagon</td>
<td>1-20 µg/kg/h i.v.</td>
<td>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.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>5-30 µg/kg/day s.c.</td>
<td>Continuous s.c. infusion or divided in 4-6 single doses</td>
</tr>
</tbody>
</table>

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

Table 4   Drug treatment – Long-term management

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

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
Neonatal hypoglycaemia indicative of CHI

Trial therapy with diazoxide for at least 5 days (up to 15 mg/kg/day)

Diazoxide unresponsive

Distinguish between focal or diffuse form

Genetically confirmed diffuse disease (homozygous or compound heterozygous mutation in ABCC8, KCNJ1 or GCK, GLUD1 mutation)

No

Perform $^{18}$FDOPA-PET/CT

Focal

Laparoscopic enucleation of focal lesion

Diffuse

Try conservative treatment with octreotide, nifedipin, frequent feeding

Resistance to medical treatment

Yes

Near-total pancreatectomy

Follow up: Growth; Neurological/psychomotoric development; Screen for diabetes mellitus and exocrine pancreas insufficiency

No

Consider trial off or reduction of medication every two years

Follow up: Growth; Neurological/psychomotoric development

Diazoxide responsive

Further diagnostic work-up for „metabolopaties“;

Genetic analysis

Consider trial off diazoxide every two years or if diazoxide dose falls <5 mg/kg/d

Follow up: Growth; Neurological/psychomotoric development

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 prospective 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 (HBA1c, 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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