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Hyperinsulinemic hypoglycemia: clinical, molecular and therapeutical novelties

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Abstract Hyperinsulinemic hypoglycemia (HI) is the most common cause of hypoglycemia in children. Impairment of cellular pathways involved in insulin secretion from pancreatic β-cells, broadly classified as channelopathies and metabolopathies, have been discovered in the past two decades. The increasing use of NGS target panels, combined with clinical, biochemical and imaging findings allows differentiating the diagnostic management of children with focal forms, surgically curable, from those with diffuse forms, more conservatively treated with pharmacological and nutritional interventions. Specific approaches according to the subtype of HI have been established and novel therapies are currently under investigation. Despite diagnostic and therapeutic advances, HI remains an important cause of morbidity in children, still accounting for 26–44% of permanent intellectual disabilities, especially in neonatal-onset patients. Initial insult from recurrent hypoglycemia in early life greatly contributes to the poor outcomes. Therefore, patients need to be rapidly identified and treated aggressively, and require at follow-up a complex and regular monitoring, managed by a multidisciplinary HI team. This review gives an overview on the more recent diagnostic and therapeutic tools, on the novel drug and nutritional therapies, and on the long-term neurological outcomes.

Keywords Hyperinsulinemic hypoglycemia · Genetics · Hypoglycemia · Neurodevelopment · Novel therapies · Nutritional interventions

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Introduction

Hyperinsulinemic hypoglycemia (HI) is the most frequent cause of severe and persistent hypoglycemia in the neonatal period and early infancy (1:20,000–1:50,000 live births, and 1:2500 in areas with high rates of consanguinity, such as Saudi Arabia) (Bruining 1990). HI is caused by uncontrolled or excessive insulin secretion for the prevailing glucose levels. Patients present with recurrent episodes of profound hypoglycemia requiring rapid and intensive treatment with high dose glucose infusions and i.v. glucagon to prevent irreversible neurological sequelae (De Leon and Stanley 2007; Kapoor et al 2009a; Arnoux et al 2011; Stanley and Matschinsky 2012; Stanley 2016). Diagnosis is defined by the finding of inappropriate unsuppressed insulin during hypoglycemia and/or by indirect signs of inappropriate insulin excess, such as suppressed circulating non-esterified fatty acids (NEFA), hypoketonemia, hyperglycemic response to glucagon and high glucose demand (De Leon and Stanley 2013; Ferrara et al 2016).

Pathophysiology

The insulin secretion from pancreatic β-cells is dependent from intracellular glucose metabolism, as summarized in

Fig. 1. As soon as glucose enters the β-cells through GLUT1 and GLUT2, it is phosphorylated by glucokinase (GCK) to glucose-6-phosphate (glucose-6-P), then converted to pyruvate through the glycolysis. Pyruvate can enter the mitochondrion and, through its oxidation in the TCA cycle, increases the ATP/ADP ratio, which causes the inactivation of the pancreatic ATP-sensitive potassium (K_{ATP}) channels. Closure of K_{ATP} channels leads to depolarization of the plasma membrane, activation of voltage-gated calcium channels, elevation of cytosolic Ca^{2+}, and release of insulin into the circulation (Stanley 2016).

Genetics and histology

In the past, diffuse HI was erroneously labeled as "nesidioblastosis," presumed to be an embryological anomaly of β-cells proliferating from ductal epithelium (Laidlaw 1938; Yakovac et al 1971). Subsequently, it became clear that nesidioblastosis is a common feature of the pancreas in normoglycemic neonates and infants, therefore the term was abandoned (Rahier et al 1981; Palladino and Stanley 2011). Currently, mutations in 11 genes have been associated with HI (Stanley 2016). Furthermore, INSR mutations have also been reported causing HI (Hojlund et al 2004). However, the causative role of INSR is still debated. They can be broadly categorized into two groups, channelopathies and metabolopathies (Dunne et al 2004), as listed in Table 1. Approximately 300 different loss-of-function mutations in *ABCC8* and 30 in *KCNJ11*, which respectively encode for the SUR1 and Kir6.2 subunits of the K_{ATP} channel (channelopathies), account for more than 60% of HI cases (De Leon and Stanley 2017; Kapoor et al 2013; Faletra et al 2013; Flanagan et al 2009; Snider et al 2013). Mutations on these two genes have been associated with two histological aspects of the endocrine pancreas. A diffuse form, affecting all β-cells, inherited as either autosomal recessive or dominant traits, and a focal form, which results from the combination of a paternally inherited germinal mutation and a somatic loss of heterozygosity of the maternal allele in a restricted group of β-cells (De Lonlay et al 1997). Histologically the two forms are different and can be easily recognized (Rahier et al 2011). A third form, defined as atypical HI, has also been described and accounts for approximately 10–15% of patients undergoing pancreatectomy. Patients with atypical form normally seek treatment later in childhood, have unknown genetic cause of

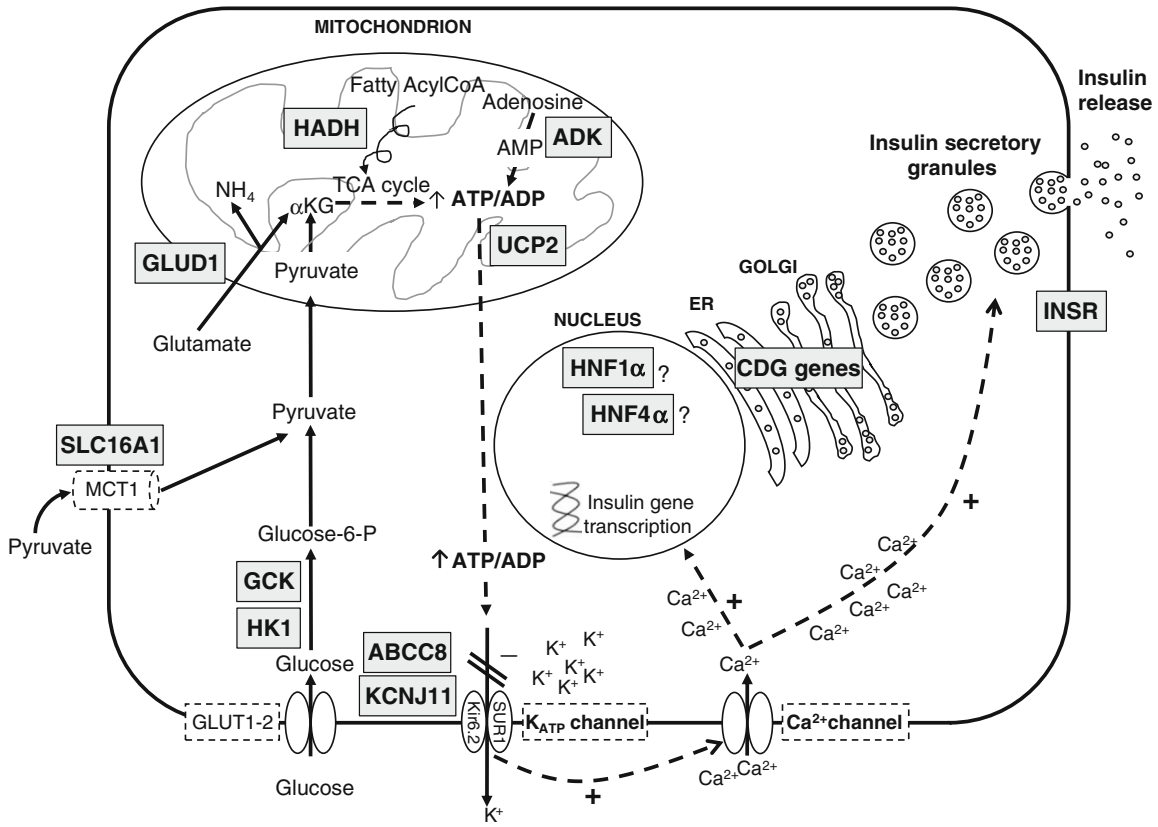

Fig. 1 Cellular pathways of insulin secretion. Blood glucose enters the β-cell through GLUT1 and GLUT2. It is phosphorylated by GCK to glucose-6-P, then fuels the glycolysis and is converted to pyruvate, which enters into the mitochondrion. Its oxidation in TCA cycle raises the ATP/ADP ratio, which is followed by the inactivation of the K_{ATP} channels. Closure of K_{ATP} channels leads to depolarization of the plasma membrane, activation of voltage-gated calcium channels and elevation of cytosolic Ca^{2+} . The rise of the intracellular Ca^{2+} concentration stimulates insulin secretion from granules and insulin transcription. Gray boxes indicate known genes causing HI

Table 1 Genetic causes of hyperinsulinemic hypoglycemia grouped into the two main categories: channelopathies and metabolopathies

Gene	Protein	Inheritance	Biomarker	Note	Gene locus MIM*	Phenotype MIM #
Channelopathies						
ABCC8	SUR1	AR-AD Sporadic (focal)		Protein sensitivity	600509	256450
KCNJ11	Kir6.2	AR-AD Sporadic (focal)		Protein sensitivity	600937	601820
Metabolopathies						
GLUD1	Glutamate dehydrogenase	AD	Hyperammonemia, α-ketoglutarate U	Leucine sensitivity	138130	606762
GCK	Glucokinase	AD			138079	602485
SCHAD	3-hydroxyacyl-CoA dehydrogenase	AR	Hydroxybutirylcarnitine 3-hydroxyglutarate U	Protein sensitivity	601609	609975
HNF1α	Hepatocyte nuclear factor 1α	AD		Macrosomia, Familial MODY3	142410	
HNF4α	Hepatocyte nuclear factor 4α	AD	Glycosuria, phosphaturia, aminoaciduria	Macrosomia, Familial MODY1, hepatic glycogenosis, renal Fanconi	600281	
SLC16A1	Monocarboxylate transporter 1	AD		Exercise induced hypoglycemia	600682	610021
UCP2	Uncoupling protein 2	AD			601693	
INSR	Insulin receptor	AD		Postprandial hyperinsulinemic hypoglycemia, insulin resistance, acanthosis, hypertrichosis	147670	609968
HK1	Hexokinase 1	AD			142600	
ADK	Adenosine kinase	AR	↑ Methionine P, ↑ SAM/SAH, adenosine ± dicarboxylic aciduria (normal acylcarnitines)	Frontal bossing, epilepsy, PM delay, hepatopathy	102750	614300
PMM2	Phosphomannomutase 2	AR	Abnormal transferrin IEF	CDG type Ia	212065	212065
MPI	Mannosephosphate isomerase	AR	Abnormal transferrin IEF	CDG type Ib	154550	602579
ALG6	Asparagine-linked glycosylation 6, alpha-1,3-glucosyltransferase homolog	AR	Abnormal transferrin IEF	CDG type Ic	604566	603147
ALG3	Asparagine-linked glycosylation 3 homolog (*S. cerevisiae*, alpha-1,3-mannosyltransferase)	AR	Abnormal transferrin IEF	CDG type Id	608750	601110
PGM1	Phosphoglucomutase 1	AR	Abnormal transferrin IEF	CDG type It	171900	614921

U: urinary

P: plasma

disease, and do not exhibit the characteristic histopathological findings of diffuse and focal HI. These forms can present as segmental mosaic forms or extensive

focal forms (Sempoux et al 2011; Capito et al 2011). More recently, analysis of post-operative pancreatic samples strongly reaffirmed the role of islet cell nucleomegaly as the hallmark of diffuse HI, when enlarged nuclei are detected in more than one-third of islets. Conversely, nucleomegaly was eight-fold lower both in focal and atypical HI, along with a higher proliferation rate (Han et al 2016). Atypical forms can be associated with somatic mutations of HK1 and GCK (Henquin et al 2013). Alterations outside the β-cells lineage imply that HI may directly affect other pancreatic lineages. Abnormal somatostatin-stained δ-cells have been reported in diffuse HI (Salisbury et al 2015).

Metabolopathies refer to genetic defects in cellular metabolic pathways that, with different mechanisms and inheritance, lead to more rare forms of diffuse HI (Table 1). Metabolopathies include genes involved in fatty acid oxidation (Molven et al 2004), in energy and aminoacid metabolism (Glaser et al 1998; Otonkoski et al 2003; Gonzalez-Barroso et al 2008; Henquin et al 2013; Pinney et al 2013; Stanley et al 1998; Staufner et al 2016), in protein glycosylation (Jaeken et al 1998; Sun et al 2005; Shanti et al 2009; Miller et al 2011; Tegtmeyer et al 2014) as well as in genes encoding for transcription factors (Pearson et al 2007; Flanagan et al 2010) and for insulin receptor (Hojlund et al 2004). More detailed descriptions of the metabolopathies are discussed in the Supplementary material. Moreover, HI has also been associated with several syndromes (Table 2). Details on novel syndromic disorders presenting HI and on molecular mechanisms of HI in patients with BWS are reported as Supplementary material.

Table 2 Syndromic forms of HI

Genetic syndromes	References
Beckwith-Wiedemann (± K_{ATP} mutation)	DeBaun et al 2000; Munns and Batch 2001; Hussain et al 2005; Kalish et al 2016
Sotos	Baujat et al 2004
Perlman	Henneveld et al 1999
Simpson-Golabi	Terespolsky et al 1995
Ondine	Meissner et al 2001; Hennewig et al 2008
Kabuki	Bereket et al 2001; Genevieve et al 2004
Usher	Bitner-Glindzicz et al 2000
Timothy	Splawski et al 2004
Costello	Alexander et al 2005; Sheffield et al 2015
Trisomy 13 (Patau syndrome)	Smith and Giacoia 1985
Turner mosaic	Alkhayyat et al 2006
AKT2	Hussain et al 2011; Arya et al 2014a; Garg et al 2015
AKT3	Nellist et al 2015
PI3KCA	De Leon and Stanley 2017
TRMT10A	Gillis et al 2014
CACNA1D	Flanagan et al 2017
Undiagnosed dysmorphisms	Meissner et al 2001

Diagnosis

The diagnosis of HI is defined by an unsuppressed detectable plasma insulin level (>2–3 μU/ml) in a critical sample collected at the time of spontaneous hypoglycemia or when plasma glucose is lower than 50 mg/dl in a diagnostic fasting test (Thornton et al 2015). Since plasma insulin concentrations are frequently not elevated, the diagnosis also relies on signs of inappropriate insulin excess, which include suppressed NEFA (<1.7 mM), hypoketonemia (<1.8 mM), a hyperglycemic response to i.m. administration of glucagon (delta glucose >30 mg/dl in 30 min) and on a high glucose demand (>10 mg/kg/min in neonates) (Arnoux et al 2011; De Leon and Stanley 2013; Ferrara et al 2016). Once HI is defined as the cause of hypoglycemia, in parallel with treatment start, the next step is the differentiation between the diffuse and focal forms which have different management and outcome, and hence differential diagnosis becomes a crucial point. In the late 1990s, pancreatic venous sampling (PVS), with measurement of insulin concentration in the pancreatic drainage veins, and selective pancreatic arterial calcium stimulation with hepatic venous sampling (ASVS) were the elective procedures to differentiate between diffuse and focal HI (De Lonlay et al 1999; Stanley et al 2004). In 2005, ^{18}F–DOPA PET/TC imaging overcame the PVS and ASVS, due to higher sensitivity, specificity, and accuracy in localizing focal lesions in the pancreas (Ribeiro et al 2005; Otonkoski et al 2006; Treglia et al 2012; Blomberg et al 2013; Laje et al 2013) or in ectopic sites (Hussain et al 2006). Focal HI is an elective indication to partial pancreatectomy, which allows the complete cure of disease. On the other hand, diffuse HI is first approached with conservative pharmacological treatment, and only when medical measures are ineffective, a near-total pancreatectomy is required. However, this procedure is often associated with later appearance of diabetes and an increased risk of exocrine pancreatic failure (De Lonlay et al 1999; Beltrand et al 2012; Arya et al 2014b; Lord et al 2015), and does not guarantee the remission of hypoglycemia (Arya et al 2014b).

Most of current diagnostic algorithms recommend ^{18}F–DOPA PET/TC only after testing the response to medical therapy, based on the assumption that focal HI is always unresponsive, therefore avoiding the procedure in patients showing a response to first line drugs (Kapoor et al 2009a, b; Arnoux et al 2011; De Leon and Stanley 2017). However, although rarely, focal HI could also be drug-responsive

(Touati et al 1998; Loechner et al 2011; Ismail et al 2012; Kapoor et al 2013; Maiorana et al 2014). Since neurological sequelae have been reported in HI patients despite long-term diazoxide therapy (Meissner et al 2003; Avatapalle et al 2013), the indication to perform ^{18}F–DOPA PET/TC is mainly driven by genetic analysis, also in diazoxide-responsive patients (Maiorana et al 2014). Indeed, the recent wide use of next generation sequencing (NGS) targeted panels, which represents a high-throughput technology for rapid genetic screening diagnosis (Ponzi et al 2016), further strengthens this diagnostic approach (Fig. 2). Preoperative diagnosis of focal HI is of great importance for clinical decision-making. Predicting the clinical phenotype of novel variants might be feasible for null mutations, such as nonsense defects, because these could only act in a recessive manner. However, the large number of novel missense mutations may lead to difficult diagnostic interpretation. They could potentially be either recessively or dominantly inherited or might also represent variants of unknown significance. Sensitivity of mutation analysis for predicting focal HI based on findings of a monoallelic recessive K_{ATP} mutation was found to be 97%, with a specificity of 90%, that slightly increased in the case of paternal inheritance (Snider et al 2013). In addition, some cases lacking mutations might have a postzygotic mutation of dominant HI genes as GCK (Henquin et al 2013). Finally, the possibility of novel genetic causes of HI is likely. Therefore, accurate and timely

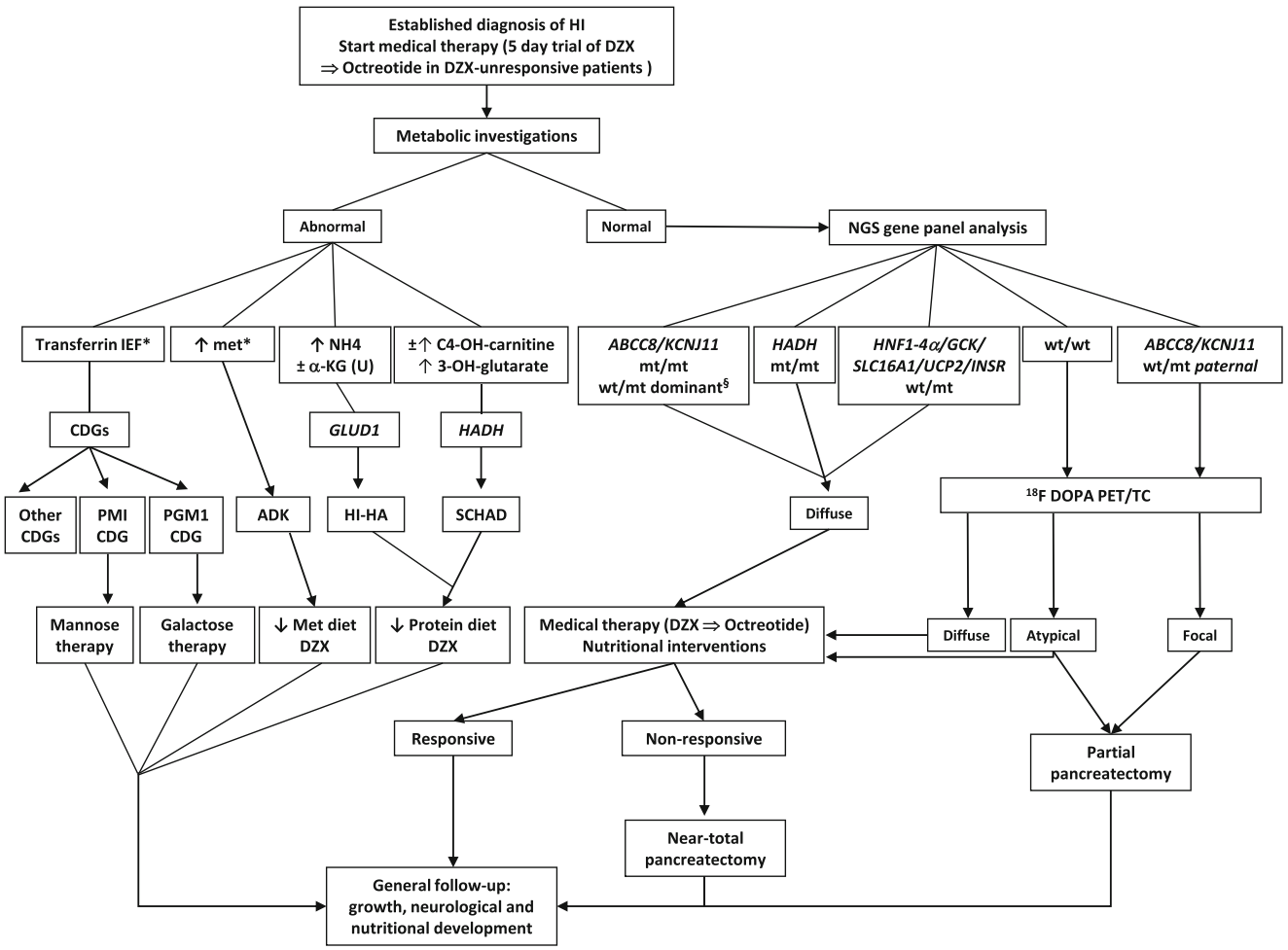

Fig. 2 Suggested diagnostic and management algorithm for HI. Once the diagnosis of HI and medical therapy have been established, a metabolic diagnostic work-up is recommended to identify specific inherited disorders which include hyperinsulinism-hyperammonemia (HI-HA) syndrome and SCHAD. As highlighted by the asterisk, the clinical phenotype may be of help in further metabolic testing to diagnose CDGs and ADK deficiency. In patients positive for metabolic biomarkers, further genetic analysis is needed to confirm diagnosis and for genetic counseling. Patients negative for metabolic biomarkers should undergo a NGS screening for known genes causing HI. When genetic analysis is consistent with the suspicion of focal HI, patients should undergo ^{18}F DOPA PET/CT to look for a focal form, which is an elective indication for partial pancreatectomy. Conversely, diffuse forms should be conservatively treated with drug and nutritional therapy. Near-total pancreatectomy should be considered only in the case of unresponsive diffuse HI. Patients with no detectable mutations (wt/wt) should also undergo ^{18}F DOPA PET/CT looking for some atypical forms, potentially treatable by limited pancreatectomy, i.e., extensive focal forms. Wt, wild type; mt, mutant; wt/mt dominant§, already reported in the literature or family tree strongly suggestive of dominant negative mutation; transferrin IEF* and aminoacids for methionine (met)*, to be performed in selected cases, according to the clinical phenotype; U, urinary; DZX, diazoxide

prediction of phenotype based on genotype through expression study and parental history is crucial to limit exposure to persistent hypoglycemia in infants and children with HI (Snider et al 2013).

Current treatment

Treatment of HI includes the emergency management of hypoglycemia and the long-term therapy.

At diagnosis, the goal of the emergency therapy is to promptly restore normoglycemia using concentrated glucose infusion. Given the high glucose demand, continuous i.v. glucagon infusion (1–2 mg/day) is helpful in maintaining normoglycemia, reducing fluids overload especially in neonates. The main goal of the long-term treatment is the prevention of neurological damage. This is obtained by maintaining normoglycemia, tailoring the optimal treatment regimen according to the patient characteristics and type of hyperinsulinism. Diazoxide is the first line drug to be attempted and is considered the mainstay long-term therapy (Aynsley-Green et al 2000). Diazoxide opens the K_{ATP} channel via SUR1 binding, thus reducing insulin secretion. It is administered perorally with a dose range of 5–15 mg/kg/day. Common side effects include hypertrichosis and fluid retention, that might cause an increased risk of heart failure, especially in pre-term newborns (Welters et al 2015). Infants on intravenous fluids are especially at risk and are likely to require intensive diuretic therapy (hydrochlorothiazide and furosemide) to control diazoxide-induced fluid retention. Diazoxide-responsiveness is defined as the ability to wean i.v. glucose infusion, while maintaining normoglycemia on a normal feeding schedule and an age-based fasting after at least 5 days from therapy initiation at a maximal dose (Arnoux et al 2011; De Leon and Stanley 2017).

In diazoxide-unresponsive patients, the second line drug is octreotide, a somatostatin analogue (Glaser et al 1989). Although not officially approved for HI (off-label use), octreotide is administered subcutaneously 3–4 times/day at the dosage of 5–20 μg/kg/day. Octreotide reduces insulin secretion with multiple mechanisms, by activating K_{ATP} channels, affecting intracellular translocation of Ca^{2+} and through a direct inhibition of insulin transcription via activation of protein kinase A (Welters et al 2015). Side effects include tachyphylaxis, site injection nodules, diarrhea and gallstones. Tachyphylaxis is probably due to down-regulation of the β-cell somatostatin receptors and often limits the efficacy of the drug. Necrotizing enterocolitis has been reported in neonates (Laje et al 2010; Reck-Burneo et al 2008; Hawkes et al 2016). Octreotide has also been associated with elevated liver enzymes, both severe and transient (Avatapalle et al 2012; Demirbilek et al 2014).

Calcium channel antagonists, such as nifedipine or amlodipine, have been anecdotally attempted in a few HI patients (Muller et al 2004). There is general consensus that these drugs are not considered as indicated because of the lack of effectiveness (Guemes et al 2017).

Unresponsive or partially responsive HI may require frequent glucose enriched oral feedings, with frequent or continuous enteral feedings (Arnoux et al 2010). Low protein diet with a reduced leucine intake, is recommended in the leucine-sensitive hyperinsulinism-hyperammonemia syndrome (Zammarchi et al 1996; De Lonlay et al 2001; Hsu et al 2001; Kelly et al 2001).

Novel drug therapies

Long-acting somatostatin-analogues

In the last few years, long-acting somatostatin-analogues (LAR-octreotide and lanreotide) have been successfully used in children over 1 year of age responsive to octreotide (Modan-Moses et al 2011; Le Quan Sang et al 2012; Kuhnen et al 2012). These analogues act through specific receptors (SST2) with K_{ATP}-dependent and independent mechanisms. The use of standard octreotide, which requires multiple subcutaneous administrations, is burdensome for long-term treatment, whereas long-acting somatostatin-analogues can be administered every 28 days, with striking advantages for patients and families. LAR-octreotide is administered i.m., its concentration raises in 7 days and remains stable for 4 weeks; lanreotide is administered deeply subcutaneously, its concentration raises quickly in a few hours and then progressively declines within the following 4 weeks. The dosage of long-acting somatostatin-analogues is equal to the cumulative dose of 30 days of octreotide (Astruc et al 2005; Modan-Moses et al 2011; Le Quan Sang et al 2012). Compared to octreotide, long-acting somatostatin-analogues allow a similar or even better glycemic control with the advantage of a single administration every 4 weeks (Kuhnen et al 2012), meaning a shift from 90 to 120 injections per month to 1 injection per month, with major improvement in quality of life. These drugs are considered for use in older infants responsive to short-acting octreotide aiming to reduce the clinical burden (less injections, easier for kindergarten, school, vacations, daily life).

Sirolimus

To avoid an extensive surgical approach in drug-unresponsive patients, sirolimus (rapamycin) has been recently attempted (Senniappan et al 2014). Sirolimus, a mTOR pathway inhibitor, is an immunosuppressive drug with current indications for post-kidney transplant immunosuppression and with an expanding use in pancreatic neuroendocrine tumors, insulinoma, leukemia, lymphangioleiomyomatosis, and

tuberous sclerosis (Boulay et al 2004; Boucier et al 2009; Kulke et al 2009; Yao et al 2010; Krueger et al 2013). The rationale for its use in HI was based on the observation that patients treated with sirolimus often presented hyperglycemia. This side effect is due to the inhibitory effect on the PI3K/AKT/mTor pathway, a nutrient sensor involved in numerous cellular processes, including cell metabolism, growth, proliferation, apoptosis, response to oxidative stress, and insulin secretion (Leibowitz et al 2008). So far, some case studies reported on the successful use of sirolimus, sometimes in combination with octreotide. However, efficacy was limited in the face of important side effects, which include immunosuppression, cytopenia, stomatitis, increased infections, transaminases elevation, and pancreatic insufficiency (Szymanowski et al 2016). Furthermore, a recent report showed very poor results in patients with severe HI, highlighting the risk of long-term severe side effects and pointing out the need to only use sirolimus in the context of a controlled clinical trial (Banerjee et al 2017).

Future promising therapies

Exendin-(9–39)

Exendin-(9–39) is a reverse agonist of glucagon-like peptide −1 (GLP-1) receptor. GLP-1 is an incretin hormone which stimulates insulin secretion in response to ingested nutrients. Chronic subcutaneous infusion of exendin-(9–39) prevented fasting hypoglycemia in SUR1$^{-/-}$ mice (De Leon et al 2008). Moreover, in vivo and in vitro studies demonstrated that exendin-(9–39) inhibited aminoacid-induced insulin secretion, in SUR1$^{-/-}$ mice and in pancreatic islet isolated from neonates with K_{ATP}-HI, respectively (De Leon et al 2008). Glutamine may mediate protein-sensitivity of K_{ATP}-HI via the "amplification" pathway of the GLP-1 receptor (Li et al 2004; De Leon et al 2008). A short-term trial conducted on 9 adolescents-adults with K_{ATP}-HI allowed a significant improvement of blood glucose levels along with a reduction of the insulin/glucose ratio (Calabria et al 2012). Similar effects have also been observed in pediatric patients, where exendin-(9–39) prevented aminoacid-induced hypoglycemia (NCT00897676, http://www.clinicaltrials.gov). A trial on the effect on glucose requirements is ongoing in infants (NCT00835328).

Subcutaneous glucagon

The use of glucagon for long-term treatment is hampered by its short half-life and because of the need of parenteral administration. Subcutaneous glucagon (via portable subcutaneous pump at a dosage of 0.026–0.8 mg/kg/day) was successfully used in a few diazoxide-unresponsive children, allowing reduction or discontinuation of central glucose infusion (Mohnike et al 2008). In patients treated with octreotide, its dosage was considerably reduced, avoiding pancreatectomy or subsequent resurgery. To prevent crystallization, an experimental glucagon technospheres suspension in aqueous solution was successfully used in 3 of these children (Mohnike et al 2008). More recently, another study reported that continuous subcutaneous glucagon infusion allowed restoration of normoglycaemia, attenuating weight gain and improving developmental skills in a patient with atypical diffuse HI with mosaic *ABCC8* mutations, still unresponsive after two subtotal pancreatectomies (Neylon et al 2013). A proof-of-concept clinical trial is ongoing in infants with diazoxide-unresponsive HI (NCT02937558).

Anti insulin receptor antibodies

Antibodies for allosteric inhibition of insulin receptor corrected fasting hypoglycemia in SUR1$^{-/-}$ mice by reducing hepatic insulin sensitivity and insulin signaling in muscle, liver, and fat tissue (Patel et al 2013) and prevented insulin-induced hypoglycemia in normal volunteers (Nath et al ENDO 2015*)*. A trial to evaluate the effect of a single dose in HI adult patients is currently ongoing (NCT02604485).

Small molecules

Rescue of K_{ATP} channel activity could be beneficial for the treatment of HI, especially if these channels retained regulatory properties or could be activated by K_{ATP} channel agonists. Obtaining a successful enhancement of K_{ATP} channel activity could eventually have an impact on clinical treatment of HI (Powell et al 2011). In vitro studies with small molecules acting as chaperones to correct K_{ATP} trafficking defects (carbamazepine and sulfonylureas) showed rescue of SUR1 protein only when mutations affected the TMD0 domain, with normal co-expression of Kir6.2 (Martin et al 2016).

Novel nutritional interventions

Ketogenic diet

Nutritional interventions could provide an important contribution in maintaining normoglycemia in HI, particularly in patients with poor drug responsiveness. Ketogenic diet (KD) is a nutritional regimen with over 60% of the total caloric intake provided by lipids. The main indication of KD in children is the treatment of refractory epilepsy (Bough and Rho 2007; Kossoff et al 2009). However, KD is also the elective treatment of GLUT1 deficiency, a disorder in which the impaired glucose transport across the blood-brain barrier causes neuroglycopenia, with consequent epilepsy, developmental

delay and movement disorders (De Vivo et al 1991; Pearson et al 2013). In GLUT1 deficiency, neuroglycopenia and CNS energy failure are bypassed by KD, which provides ketone bodies as an alternative energy source for the brain (De Vivo et al 1991). In HI, insulin excess induces severe hypoglycemia with consequent neuroglycopenia. Moreover, the availability of alternative energetic substrates for the CNS is further reduced, because of the concomitant inhibition of gluconeogenesis, glycogenolysis, and lipolysis. Based on the similarities of brain metabolism perturbation shared by GLUT1 deficiency and HI, we successfully utilized KD in a patient with severe drug-resistant GCK-HI, presenting recurrent hypoglycemia, refractory epilepsy, and mild intellectual disability (Maiorana et al 2015). While maintaining blood ketones between 2 and 5 mmol/L, KD fully resolved neuroglycopenic signs, with disappearance of epilepsy, improvement of EEG and cognitive abilities. Definitely, the availability of an alternative cerebral energy source improved neurodevelopment, avoiding the need of near-total pancreatectomy (Maiorana et al 2015). Although based on a single experience, KD could represent an effective treatment to support brain function in selected cases of unresponsive HI.

Galactose therapy in PGM1-CDG

Phosphoglucomutase 1 (PGM1)-CDG has been recently reported as a novel disease, bridging CDGs and glycogen storage diseases (Morava 2014; Tegtmeyer et al 2014). PGM1 catalyzes the transfer of phosphate between glucose-1-P and glucose-6-P. Patients with recessive mutations in PGM1 manifest a complex phenotype characterized by hepatopathy, bifid uvula, growth retardation, myopathy, cardiomyopathy, coagulation and endocrine alterations. Patients show a combination of fasting ketotic hypoglycemia, with post-prandial hyperinsulinemic hypoglycemia. Although not fully supported by strong evidence, the proposed mechanisms were impaired carbohydrate metabolism for the first condition, and a lower glucose threshold for insulin secretion caused by the increased glucose-6-P for the latter. Therapy with oral galactose at the dosage of 1 g/kg/day improved hypoglycemia, coagulation, and endocrine abnormalities as well as transferrin glycosylation pattern (Morava 2014; Tegtmeyer et al 2014).

Long-term neurological outcome

Hyperinsulinemic hypoglycemia is an important cause of brain injury in children, leading to long-term neurological impairment with intellectual disability, epilepsy, blindness and cerebral palsy. In HI, the major vulnerability of brain in early life is related to the lack of energy substrate for cerebral activity, which is mainly dependent on glucose, accounting for 40–60% of basal metabolic rate (Holliday 1971; Goyal et al 2014). Moreover, insulin excess further impairs CNS energy failure by suppressing the availability of alternative substrates. The topographic distribution of brain lesions is determined by patients age, reflecting the physiological timing of brain maturation: posterior white matter in neonates, basal ganglia in infants, and parieto-temporal cortex in children (Gataullina et al 2013). As shown in Table 3, most reports on the neurological outcome in large HI series, which often include non-homogenous cohorts (genotypic and phenotypic heterogeneity, combination of medical and surgical treatments, patients treated before the systematic use of octreotide, ages of subjects, and source of data, i.e., parental interview or psychometric tests), showed that developmental delay ranges from 26%

Table 3 Neurological outcome in large series of patients with HI

	Menni 2001	Meissner 2003	Steinkrauss 2005	Avatapalle 2013	Lord 2015	Salomon-Estebanez 2016	OPBG series
Patient N°	90	114	68	67	121 surgically treated only	21	50
Severe DD %	8	18	16	27			2
Moderate DD %	18		15				2
Mild DD %		26		12	27	38	28
Epilepsy %	18	25			13		8

DD: developmental delay

OPBG: Bambino Gesù Children's Hospital

to 44%, and epilepsy accounts for 18–25% (Menni et al 2001; Meissner et al 2003; Steinkrauss et al 2005; Avatapalle et al 2013). In a more recent study conducted on K_{ATP}-HI patients treated with both diazoxide or somatostatin-analogues, mild developmental delay was observed in 38% of children (Salomon-Estebanez et al 2016). Remarkably, the proportion of children with neurodevelopmental outcomes was similar in subjects with spontaneous disease remission when compared to those with persistent HI and, surprisingly, 75% of the most severe K_{ATP}-patients had normal neurodevelopment (Salomon-Estebanez et al 2016). Another recent study, focused on the neurocognitive outcome in subjects treated with near-total pancreatectomy, 48% of patients showed neurobehavioral signs (i.e., speech delay, learning disabilities, seizures, physical disabilities, ADHD, autism), combined with a high risk of developing diabetes (36%) and no outcome differences between patients diagnosed before and after 2004, when ^{18}F DOPA PET imaging was undertaken (Lord et al 2015). We retrospectively evaluated a cohort of 50 patients followed at the Bambino Gesù Children's Hospital in Rome and found a rate of developmental delay similar to the report of Menni (2001), with a predominance of mild delay (28%, of whom 12% were borderline and 16% mild). Epilepsy was less frequently recorded (8%) and prevailed in patients with hyperinsulinism-hyperammonemia syndrome, a condition with a higher incidence of epilepsy and neurological disabilities (Bahi-Buisson et al 2008). The incidence of drug-unresponsiveness was lower in our series, but the strict monitoring at follow-up based on serial use of the continuous glucose monitoring system (Maiorana et al 2014) combined with individualized pharmacological and nutritional interventions, might have contributed to a more favorable neurological outcome (Table 3 and Supplementary material). Definitely, despite diagnostic and therapeutic advances, HI still represents an important cause of brain injury. Therefore, based on the principle that hypoglycemia in the first days of life greatly contribute to the poor outcomes (Lord et al 2015), we recommend to increase the awareness of neonatologists and pediatricians to improve early diseases recognition, allowing a rapid and aggressive treatment, before the appearance of irreversible neurological damage (Thornton et al 2015). At follow-up, patients require regular and strict monitoring, with serial use of continuous glucose monitoring (Maiorana et al 2014). Longitudinal evaluations should also include neurodevelopmental testing to identify children who need intervention and therapy (De Leon and Stanley 2017).

Conclusions

In conclusion, HI is the most frequent form of hypoglycemia in infancy, still causing long-term neurological sequelae. The increasing use of NGS will be of great help for the diagnosis, and the use of whole exome or genome sequencing should be encouraged for patients negative at the NGS, with the aim to discover new genes causing HI. New disease pathways have recently been discovered and novel drug and nutritional therapies are now available. Maintenance of normoglycemia is the mainstay of therapy to protect brain development, especially in early life. A multidisciplinary team is essential to diagnose, treat, and follow children with HI.

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Compliance with ethical standards

Conflict of interest A. Maiorana and C. Dionisi-Vici declare that they have no conflict of interest.

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