

Hyperinsulinemic Hypoglycemia in Infancy: Current Concepts in Diagnosis and Management

SHRENIK VORA, SURESH CHANDRAN, VICTOR SAMUEL RAJADURAI AND #KHALID HUSSAIN

From Department of Neonatology, KK Women's and Children's Hospital, Singapore; and #Genetics and Epigenetics in Health and Disease Genetics and Genomic Medicine Programme, UCL Institute of Child Health, Great Ormond Street Hospital for Children, 30 Guilford Street, London, UK.

Correspondence to: Dr Shrenik Vora, Senior Staff Registrar, Department of Neonatology, KK Women's and Children's Hospital, 100, Bukit Timah Road, Singapore 229899. vora.shrenik@kkh.com.sg

Purpose: Molecular basis of various forms of hyperinsulinemic hypoglycemia, involving defects in key genes regulating insulin secretion, are being increasingly reported. However, the management of medically unresponsive hyperinsulinism still remains a challenge as current facilities for genetic diagnosis and appropriate imaging are limited only to very few centers in the world. We aim to provide an overview of spectrum of clinical presentation, diagnosis and management of hyperinsulinism.

Methods: We searched the Cochrane library, MEDLINE and EMBASE databases, and reference lists of identified studies.

Conclusions: Analysis of blood samples, collected at the time of hypoglycemic episodes, for intermediary metabolites and hormones is critical for diagnosis and treatment. Increased awareness among clinicians about infants "at-risk" of hypoglycemia, and recent advances in genetic diagnosis have made remarkable contribution to the diagnosis and management of hyperinsulinism. Newer drugs like lanreotide (long acting somatostatin analogue) and sirolimus (mammalian target of rapamycin (mTOR) inhibitor) appears promising as patients with diffuse disease can be treated successfully without subtotal pancreatectomy, minimizing the long-term sequelae of diabetes and pancreatic insufficiency. Newer insights in understanding the molecular and histological basis and improvements in imaging and surgical techniques will modify the approach to patients with congenital hyperinsulinism.

Keywords: Congenital hyperinsulinism, Diazoxide, Insulin-secreting cells

Hyperinsulinemic hypoglycemia has increasingly been recognized as a cause of intractable hypoglycemia in neonates and infants. Hyperinsulinemic hypoglycemia occurs due to unregulated insulin secretion from β -cells of pancreas in relation to blood glucose levels [1]. Small for gestational age (SGA) infants and macrosomic infants born to diabetic mothers (IDM) are the two most common groups of infants at risk of hypoglycemia in the neonatal period [2]. Glucose is the principal energy source for the neonatal brain and hypoglycemia is known to cause irreversible neuronal injury when it is recurrent and severe; so prompt recognition and treatment of these infants with hyperinsulinemic hypoglycemia is paramount [3]. Hyperinsulinemic hypoglycemia can be transient, prolonged or persistent (congenital). Knowledge of blood glucose homeostasis and appropriate investigations for intermediary metabolites during an episode of hypoglycemia is the cornerstone for diagnosis and management of hyperinsulinemic hypoglycemia. The management of medically unresponsive hyperinsulinemic hypoglycemia still remains a challenge. Knowledge of the genetic mutations, newer imaging modalities like Fluorine 18L-3, 4-dihydroxyphenylalanine positron emission

tomography (^{18}F -DOPA-PET) scan and availability of histological differentiation of focal and diffuse forms of persistent hyperinsulinemic hypoglycemia has streamlined the management of congenital hyperinsulinemic hypoglycemia (CHI) [4]. The purpose of this review is to provide an overview of physiology of insulin secretion, controversies regarding definition of hypoglycemia, spectrum of clinical presentation, and recent advances in diagnosis and management of different forms of hyperinsulinism.

GLUCOSE HOMEOSTASIS

Normoglycemia is maintained by a balance between the insulin secretion following food intake and response of the counter regulatory hormones (glucagon, growth hormone, adrenaline and cortisol) in the face of hypoglycemia. Insulin promotes peripheral uptake of glucose and counter regulatory hormones increase hepatic glucose output by glycogenolysis followed by gluconeogenesis. Liver glycogen stores in a healthy full-term infant last for 10-12 hours from birth. Endocrine changes occur soon after birth with a decrease in plasma levels of insulin and increase of catecholamine and glucagon [5]. Hepatic glucose production in a full-term infant is 4-6 mg/kg/min and the

infant switches on the endogenous production of glucose following birth until exogenous nutritional supply is established. The newborn infant has essential enzymes needed for gluconeogenesis from alanine, pyruvate, glycerol, and lactate. Soon after birth hepatic glycogenolysis provides glucose whereas β -oxidation of fatty acids and lactate generation due to proteolysis provide an adequate substrate for gluconeogenesis [6]. Infants with disorders of glycogenolysis present after 4-5 hours of fast whereas infants with disorders of gluconeogenesis become hypoglycemic after an overnight fast. On the contrary, infants with hyperinsulinism present with hypoglycemia at any time after the last feed [7].

Insulin Release from β -cells of Pancreas

Knowledge of insulin secretion by β -cells of pancreas in response to plasma glucose helps to understand the pathogenesis and management of hyperinsulinemic hypoglycemia. As shown in **Fig.1**, the metabolism of glucose, amino acids and fatty acids results in the generation of metabolic coupling factors like ATP and β -ketoglutarate, which are involved in regulating insulin exocytosis. Under normal physiological conditions, each of these coupling factors plays a key role in regulating insulin secretion precisely to keep fasting blood glucose concentrations between 3.5-5.9 mmol/L. As blood glucose level rises after feed or glucose infusion, it triggers insulin secretion from pancreatic β -cells. The GLUT2 transporters present on pancreatic β -cells facilitate the uptake of glucose. Glycolytic phosphorylation by glucokinase (GK) enzyme follows leading to a rise in the ATP:ADP ratio. Functional integrity of the pancreatic ATP sensitive potassium (K_{ATP}) channel depends on the interactions between the pore-forming inward rectifier potassium channel subunit (KIR6.2) and the regulatory sulfonylurea receptor 1 (SUR1), encoded by *KCNJ11* and *ABCC8* genes, respectively. The increase in the cytosolic ATP:ADP ratio activates plasma membrane SUR1, which leads to the closure of K_{ATP} channel. This in turn depolarizes the membrane allowing calcium ions to flow in to the cell via voltage-gated calcium channels. Following this, the insulin storage granules undergo exocytosis resulting in release of insulin [8]. Insulin secretion is also regulated by metabolic signals arising from lipid and amino acid metabolism mediated through its effect on glutamate dehydrogenase (GDH) [9].

DEFINITION OF HYPOGLYCEMIA

Definition of hypoglycemia and screening guidelines in neonatal period remain controversial. Following severance of the umbilical cord at birth, glucose supply from the mother to the neonate ceases leading to a rapid fall in neonatal glucose concentration. Glucose level decreases

reaching a nadir at 1 hour of age and then stabilizes by 3 hours of age spontaneously or in response to milk feeds in healthy full-term infants.

In a comprehensive review of the literature in 1997, an expert panel of the World Health Organization concluded that there are numerous approaches to defining normoglycemia, including the statistical, metabolic, neurophysiological, and, perhaps most importantly, the neurodevelopmental approach. These different approaches towards definition of normoglycemia contribute to the controversy that surrounds this issue [10]. Current consensus by world experts on hyperinsulinism states that hypoglycemia cannot be defined as a specific plasma glucose concentration due to inability to identify a single value that causes brain damage and brain responses varies by the presence of alternative fuels like ketones [11]. Currently the most common practice is to screen the at-risk infants, which includes IDM and neonatal conditions like SGA (birth weight <10th centile), large for gestational age (LGA, birth weight >90th centile), perinatal asphyxia, prematurity, infection, and dysmorphic infants suggestive of Beckwith-Wiedemann syndrome. This has led to the development of guidelines designed to identify infants "at-risk" and the implementation of an "operational threshold" for physicians to consider intervention [12].

In 2011, clinical report of the American Academy of Pediatrics recommended screening of "at-risk" infants within first hours of birth. The macrosomic IDM, late-preterms (34 to 36⁺⁶ weeks gestation) and SGA infants should be fed every 2-3 hours with estimation of pre-feed

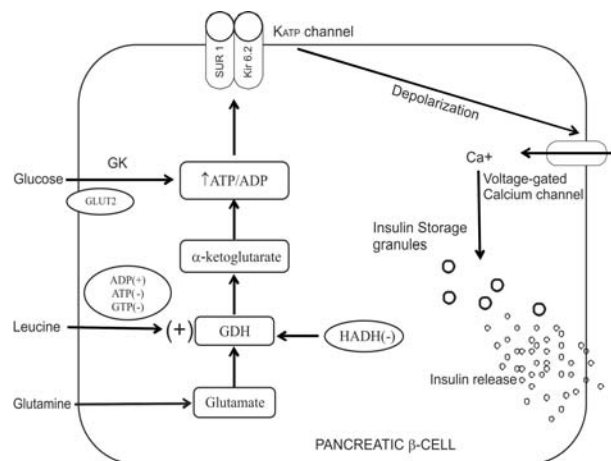


FIG. 1 Glucose and Protein mediated insulin secretion from β -cells of pancreas.

GDH: Glutamate dehydrogenase; HADH: L3-hydroxyacyl-CoenzymeA dehydrogenase; GK: Glucokinase; SUR 1: Sulfonylurea receptor; Kir6.2: Potassium channel inwardly rectifier; GLUT2: Glucose transporter 2

glucose levels for multiple feed-fast cycles for at least 24 hours. Further monitoring of blood sugar levels should be continued only if plasma glucose levels remain below 2.5 mmol/L. Symptoms in infants with blood glucose value less than 2.2 mmol/L warrant parenteral glucose infusion. In asymptomatic infants, a practical approach based on age, risk factors and mode of feeding can be considered when treatment is planned. Any infant with persistent or recurrent hypoglycemia should be screened for hyperinsulinism [13]. Hyperinsulinemic hypoglycemia is defined as inappropriately elevated plasma insulin concentration in the presence of hypoglycemia (<3.5 mmol/L) in infants receiving glucose infusion rate (GIR) of more than 8mg/kg/min, with suppressed ketone bodies and free fatty acids and a positive glycemic response to parenteral glucagon. In infants with suspected hyperinsulinemic hypoglycemia, due to lack of alternative energy fuels the blood glucose levels should be maintained >3.5 mmol/L [14].

TYPES OF HYPERINSULINEMIC HYPOGLYCEMIA

Hyperinsulinemic hypoglycemia can be transient, prolonged or persistent (congenital).

Transient Hyperinsulinemic Hypoglycemia

This is observed often in IDM, SGA infants and in infants who had perinatal asphyxia, polycythemia and Rh isoimmunization. There is no clear definition of the precise duration of transient hypoglycemia. Hyperinsulinemic hypoglycemia usually presents soon after the birth and settles within a few days responding to increment of feeds or to increasing glucose infusion rate until the β -cell insulin secretion is normalized [15].

Prolonged Hyperinsulinemic Hypoglycemia

Some of the SGA infants develop a syndrome of prolonged hyperinsulinemic hypoglycemia requiring high GIR to maintain normoglycemia and responding to medical treatment with K_{ATP} channel agonist (diazoxide). The etiology of prolonged hyperinsulinemic hypoglycemia in SGA infants could be due to a lack of supply of exogenous substrate, depletion of hepatic glycogen stores, defective gluconeogenesis, hyper-insulinism due to transient alteration in the regulation of β -cell insulin secretion, increased sensitivity to insulin or adrenocortical insufficiency. No genetic cause has been identified in prolonged hyperinsulinemic hypoglycemia and in most of the cases, resolution is observed in several weeks to months. The incidence of prolonged hyperinsulinemic hypoglycemia is reported to be as high as 1:12,000 births. There are few reports where the prolonged hyperinsulinemic hypoglycemia was diagnosed as late as 2 weeks after birth (range: 2-180 days) and hence there is a risk involved in early discharge of these SGA infants [16].

Congenital Hyperinsulinism (CHI)

CHI is a heterogeneous condition presenting with hyperinsulinism, hypoketonemia, and hypo-fattyacidemia with severe and persistent hypoglycemia. The etiopathogenesis of CHI can be due to two major defects known as channelopathies and metabolopathies. Channelopathies refer to defects in the pancreatic β -cell ATP-sensitive K_{ATP} channel that lead to unregulated insulin secretion, the commonest genetic cause being autosomal recessively inherited inactivating mutation in *ABCC8* and *KCNJ11* (chromosome 11p15.1) genes [17]. Metabolopathies cause congenital hyperinsulinemic hypoglycemia either by altering the concentration of intracellular signaling molecules (such as ATP/ADP) or by accumulation of intermediary metabolites, triggering insulin release. The commonest cause for metabolopathies is Hyperinsulinism-Hyperammonemia (HI/HA) syndrome. The incidence of CHI is estimated to be 1:40,000-50,000 in the general population, but in familial forms it may be as high as 1:2500 in populations with substantial consanguinity [18].

Genetics of congenital hyperinsulinism

Genetic defects in key genes regulating insulin secretion causes CHI. Mutations in nine genes – *ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *SLC16A1*, *HNF4A*, *HNF1A*, *UCP2* – have been identified to cause CHI, altering the β -cell function [19].

Histologically, focal and diffuse forms have been reported. Diffuse forms are inherited in an autosomal recessive or dominant manner and focal forms are sporadic in nature.

CHI due to channelopathies: Recessive inactivating mutations in *ABCC8* and *KCNJ11* genes are the most common causes of CHI and these mutations are found in 50% of the patients. These mutations alter the function of K_{ATP} channel, causing unregulated insulin secretion. This results in severe CHI and is unresponsive to K_{ATP} channel agonist, diazoxide. Histologically, recessive K_{ATP} channel mutation is characterized by large β -cells with enlarged nuclei. A milder form of CHI has been reported with dominant inactivating mutations in *ABCC8* and *KCNJ11* genes. These milder forms are also reported to be mostly unresponsive to diazoxide. In *ABCC8* gene about 150 homozygous, compound heterozygous and heterozygous inactivating mutations and in *KCNJ11* around 24 mutations have been reported [20].

Focal lesions due to K_{ATP} mutations are confined to restricted areas of pancreas. Chromosome 11p15.5 (in close proximity to K_{ATP} channel gene 11p15.1) has maternally expressed tumor suppressors *H19* and *CDK1C*

and paternally expressed growth factor gene, *IGF2*. Genetically focal lesion arises following a paternally inherited, monoallelic mutation in one of the K_{ATP} channel genes. During the development of pancreas, when segmental paternal uniparental disomy occurs as a somatic mutation, K_{ATP} channel activity is lost in the β cell. These cells also lose maternally expressed tumor suppressor activities of *H19* and *CDK1C* and the activity of paternally expressed *IGF2* is doubled, promoting the growth of abnormal β -cells. Histology reveals focal enlargement of β -cell with large nuclei. Generally (96.2%) focal lesions are unresponsive to diazoxide but are curable by limited excision [7, 18, 21].

HI/HA syndrome: It is the second commonest form of CHI, caused by activating missense mutation of the *GLUD1* gene, which encodes the mitochondrial enzyme GDH. GDH is expressed in pancreatic β -cells, liver, kidney and brain. *GLUD1* gene mutations lead to a gain of GDH function by reducing its sensitivity to allosteric inhibition by GTP and ATP, resulting in activation of insulin secretion by the amino acid leucine. Mechanism of hyperammonemia in HI/HA syndrome is unclear, may be due to increased hepatic GDH activity and ammonia synthesis or due to abnormal muscle catabolism. Recently, renal ammoniogenesis has been implicated as a source of HA [22]. Hyperammonemia, a characteristic biochemical marker of HI/HA syndrome, is typically mild to moderate in infants and is not associated with lethargy or coma. Some of these patients may not have hyperammonemia and it could be due to mosaicism for the mutation in the liver, where the mutation is absent or seen in <50% in hepatocytes. Infants with HI/HA syndrome experience both fasting and postprandial hypoglycemia following leucine intake usually after first few months of life. Diazoxide remains the mainstay of treatment in patients with HI/HA syndrome [23].

Hydroxyacyl Coenzyme A Dehydrogenase (HADH) gene mutation: Short-chain-3-hydroxyacyl-CoA dehydrogenase (SCHAD), encoded by the gene *HADH*, catalyses the penultimate reaction of the β -oxidation cycle [24]. *HADH* is expressed in pancreatic β -cells, indicating a vital role in insulin secretion. In patients with *HADH* gene mutation, "protein to protein" interaction is lost between GDH and SCHAD causing leucine-induced hyperinsulinemic hypoglycemia via a novel pathway not involving GTP regulation of GDH. The clinical phenotype of *HADH* mutations varies from mild to severe neonatal hyperinsulinemic hypoglycemia with raised levels of fatty acid metabolites responding to diazoxide [25].

Glucokinase – Cytosolic enzyme defects: Glucokinase (GCK) is a glycolytic enzyme and plays an important role

as a glucose sensor in the pancreatic β -cell controlling glucose regulated insulin secretion. Heterozygous activating mutations have been reported to cause CHI and inactivating monoallelic mutations causing mild form of diabetes (GCK-MODY). Inappropriate insulin secretion following heterozygous activating mutations of glucokinase resulted from increased affinity of the enzyme for glucose, raising the ATP: ADP ratio in the β -cell [26]. Affected patients present with fasting hypoglycemia and can be symptomatic anytime from infancy to adulthood. Mostly this form of hyperinsulinemic hypoglycemia is diazoxide-responsive but cases requiring octreotide and subtotal pancreatectomy have been reported.

Mutations in mitochondrial uncoupling protein 2 (UCP2) gene: *UCP2* acts as a negative regulator of insulin secretion of β -cells. It has been shown that *UCP2* uncouples mitochondrial oxidative phosphorylation from ATP generation. Loss of function mutation of *UCP2* gene has been reported to cause transient hyperinsulinemic hypoglycemia or mild fasting diazoxide responsive CHI [26, 27].

HNF4A/HNF1A gene mutations: *HNF4A* gene encodes for a transcription factor HNF4 α (hepatocyte nuclear factor 4 α), a member of the nuclear hormone receptor superfamily. Mutations in *HNF4A* gene are uncommon causes of hyperinsulinemic hypoglycemia, which can be either transient or persistent. *HNF4A* is required in the pancreatic β -cell for the regulation of the pathway of insulin secretion, heterozygous mutations of which cause maturity-onset diabetes of the young type 1 (MODY1) [28]. Exact mechanism of hyperinsulinemic hypoglycemia due to *HNF4A* gene mutations is unclear. The possible mechanisms might be a reduction in expression of the potassium channel subunit (Kir6.2) or reduction in expression of nuclear PPAR α (peroxisome proliferator-activated receptor α), which can shift energy metabolism in cells towards fatty acid oxidation (FAO). Similar to *HNF4A*, *HNF1A* mutations can cause hyperinsulinism in newborn and infancy, and diabetes in later life [29].

Exercise-induced hyperinsulinemic hypoglycemia (SLC16A1 gene mutation): This is a dominantly inherited form of CHI characterized by inappropriate insulin secretion following anaerobic exercise or pyruvate load. In normal physiological status, lactate and pyruvate transport into the α -cell is mediated by monocarboxylase transporter 1 (MCT1), which is encoded by the *SLC16A1* gene. Under normal circumstances, MCT1 expression in the pancreatic α -cell is very low, minimizing the effects of pyruvate and lactate on insulin secretion. Increased levels of MCT1 due to promoter-activating mutations in *SLC16A1* gene permits entry of circulating lactate and pyruvate into the β -cell,

leading to an increase in ATP generation, triggering insulin release by closure of K_{ATP} channel and depolarization of the cell. Affected children become hypoglycemic typically 30-45 minute after a period of intensive anaerobic exercise due to lactate and pyruvate accumulation [19,30]. Exercise-induced hyperinsulinemic hypoglycemia is not observed in neonates and reported cases are limited to older children and adults.

Other causes of hyperinsulinemic hypoglycemia: Rarely, hyperinsulinemic hypoglycemia is also seen associated with overgrowth syndromes like Beckwith-Wiedemann and Sotos syndromes and metabolic conditions like congenital disorder of glycosylation (CDG) and tyrosinemia. Beckwith-Wiedemann syndrome, the most common syndrome associated with hyperinsulinemic hypoglycemia is characterized by overgrowth, macroglossia, hemi-hypertrophy and abdominal wall defects. The hypoglycemia can be asymptomatic transient to rarely prolonged, extending beyond neonatal period [31]. CDG type 1b (phosphomannose-isomerase deficiency), perhaps causing abnormal glycosylation of K_{ATP} channel, causes hyperinsulinism and that may explain the response of hyperinsulinemic hypoglycemia in these infants to diazoxide [32]. The mechanism of hyperinsulinemic hypoglycemia in tyrosinemia type 1 is still unclear but may be due to accumulation of toxic metabolites causing islet-cell hyperplasia [33].

CLINICAL PRESENTATION

Patients with hyperinsulinemic hypoglycemia present during the newborn period most often during the first 24-48 hours of life. However, different studies showed median age of presentation ranging from hours to weeks. Symptoms of hypoglycemia are mostly non-specific such as lethargy, poor feeding, apnea, jitteriness, irritability, high-pitched cry, exaggerated reflexes, seizures and coma. Presentation of persistent hyperinsulinemic hypoglycemia is more severe needing higher concentrations of glucose to maintain the blood glucose level [34]. High index of suspicion, early diagnosis and aggressive management is essential to prevent unexplained deaths and brain injury due to hypoglycemia.

Neonatal Hypoglycemic Brain Injury (NHBI): Hypoglycemia, being a surrogate marker of neuronal energy deficiency, is a major cause of brain injury. Speculated mechanisms of cellular injury includes; excitatory neurotoxins active at N-methyl-D-aspartate receptors, increased mitochondrial free radical generation and initiation of apoptosis. Several neuroprotective mechanisms are believed to play a role to guard against these neuronal injuries by substitution of alternative cerebral substrates like lactate, ketone bodies, pyruvate,

amino acids, free fatty acids and glycerol [35]. It has been postulated that immature newborn brain requires decreased cerebral energy fuels as compared to children and adults. Also limited glycogen stores in astrocytes provide immediate supply of glucose to the neurons. These mechanisms can protect the brain for limited periods and permanent damage occurs if recurrent protracted hypoglycemia prevails [36]. An increased risk of cerebral palsy, development delay and low mental scores at 18 months of age has been shown in infants with recurrent hypoglycemia lasting for five or more days. Pathological changes of NHBI include swelling of the neuronal and glial cells, necrosis, gyrus atrophy and white matter demyelination [37]. Neonatal hypoglycemic brain injury predominantly affects parieto-occipital regions as evidenced by MRI scans [38].

DIAGNOSIS

A detailed history related to pregnancy (diabetes/diet/insulin), delivery (asphyxia), gestational age and birth weight (SGA/LGA/macrosomia) is essential. Parental consanguinity, family history of diabetes, and history of siblings having infantile seizures may indicate inherited cause of the hypoglycemia. A thorough physical examination of the infant to look for dysmorphic features (e.g. omphalocele, hemihypertrophy, macroglossia), evidence of hypopituitarism (e.g. cleft lip/palate, micropenis, short stature), adrenal insufficiency (e.g. hyperpigmentation, weight loss) and disorders of glycogenesis (e.g. hepatosplenomegaly) has to be carried out. Sudden cardio-respiratory arrest and acidosis with hypoglycemia in an otherwise healthy infant might point towards a metabolic disorder [39]. As mentioned

BOX 1 INVESTIGATIONS FOR SUSPECTED HYPERINSULINEMIC HYPOGLYCEMIA

Urine	Blood
Reducing substances	Glucose
Ketone bodies	Insulin / C-peptide
Amino acids	Ketone bodies
Organic acids	Free fatty acids
	Amino acids
	Lactate
	Ammonia
	Bicarbonate
	Blood gas analysis
	Inborn error of metabolism (IEM) screen
	Acyl carnitine profile
	Cortisol
	Growth hormone
	Insulin Growth Factor Binding Protein 1 (IGFBP1)

previously, “at-risk” groups of infants should be screened for hypoglycemia in relation to the risk factors specific to the individual case. Any patient with recurrent or persistent hypoglycemia despite GIR of $>8\text{mg/kg/min}$ is indicative of hyperinsulinemic hypoglycemia. The key feature of hyperinsulinemic hypoglycemia is detectable serum insulin and/or C-peptide levels during episodes of hypoglycemia along with hypoketonemia and hypofattyacidemia. When diagnosis is in doubt, a positive glycemic ($>1.5\text{mmol/L}$) response to glucagon or octreotide therapy gives a supportive evidence of hyperinsulinemic hypoglycemia [40]. Harris, *et al.* [41] showed a good correlation between continuous interstitial glucose monitoring and blood glucose measurements. Reports suggest that continuous interstitial glucose monitoring can potentially be advantageous in measuring the duration, severity, and frequency of low glucose concentrations in high-risk infants and can help identify and prevent unwanted periods of hypoglycemia or hyperglycemia [42]. To aid in the diagnosis, further assessment of plasma and urine metabolic profile (**Box 1**) and genetic testing need to be done in some infants presenting with more subtle forms of CHI, after liaising with local tertiary centres [43]. Additional provocation tests (leucine / protein loading or exercise testing) are indicated in those patients with protein/leucine sensitivity and exercise-induced hypoglycemia.

MANAGEMENT OF HYPERINSULINEMIC HYPOGLYCEMIA

The management of patients with hyperinsulinemic hypoglycemia can be extremely complicated, particularly in prolonged and persistent hyperinsulinemic hypoglycemia. They will require frequent blood glucose monitoring and the insertion of a central venous catheter to deliver concentrated dextrose infusion. Ideally, these patients should be managed at specialized centers that have the necessary multidisciplinary team experience and expertise [44]. Expert review suggests that the goal of treatment for “at-risk” infants without suspected CHI should be to maintain blood glucose levels $>2.8\text{mmol/L}$ for those aged <48 hours and $>3.3\text{mmol/L}$ for those aged >48 hours. For neonates with suspected CHI, recommendation is to keep blood glucose levels $>3.9\text{mmol/L}$ [11].

The treatment of hyperinsulinemic hypoglycemia involves medical therapy, and surgery in some cases. The mainstay of initial medical treatment is the provision of adequate carbohydrate to maintain normoglycemia i.e. blood sugar level between $3.5\text{--}6\text{mmol/L}$. Sometimes, to ensure regular frequent feeds, feeding via naso-gastric tube or feeding gastrostomy may be needed. Symptomatic hypoglycemia is treated with “minibolus” of intravenous 10% dextrose at 2mL/kg to achieve normoglycemia and higher dextrose concentrations should be avoided as bolus

to prevent rebound hypoglycemia by further stimulating insulin secretion. This is followed by gradually increasing GIR depending on blood sugar levels by using intravenous glucose at high concentrations [45].

Diazoxide, a K_{ATP} channel agonist, is the mainstay of medical treatment in prolonged hyperinsulinemic hypoglycemia. It prevents α -cell membrane depolarization and inhibits insulin secretion by keeping K_{ATP} channels open. It is given orally in the dose of $5\text{--}20\text{mg/kg/day}$ in 3 divided doses. When using diazoxide in infants having hepatic dysfunction or hypoalbuminemia, use lower doses of 3mg/kg/day as it is highly protein bound ($>90\%$). Also lower doses are safer in SGA infants as they are very sensitive to diazoxide [46]. Diazoxide is usually combined with thiazide diuretics to counteract its most common side effect of fluid retention in neonates [1]. Hypertrichosis is another important common complication of diazoxide which usually reverts following cessation of therapy. Diazoxide responsiveness is noted when infant can fast appropriately for age, maintains normal glucose levels and shows rise in serum fatty acids and ketone bodies at the end of fast [36,40]. Nifedipine, a calcium channel blocker, has been used in few diazoxide unresponsive cases of CHI, but vast majority of such patients fail to show any response [47].

Octreotide, a somatostatin analogue causing inhibition of insulin release by activation of somatostatin receptor-5, stabilizing K_{ATP} channel and inhibition of calcium mobilisation is used in resistant cases. It is given as 6-8 hourly subcutaneous injections in a dose of $5\text{--}25\text{mcg/kg/day}$ [48]. Recently, few articles suggest once-a-month intramuscular treatment with long-acting release octreotide (Lanreotide) as a simple, cost-effective and efficient alternative to thrice daily octreotide [49]. Glucagon is primarily used for management of acute symptomatic hypoglycemia as subcutaneous injection at dose of $0.5\text{--}1\text{mg}$ in cases where intravenous access is difficult. It is also used as continuous intravenous infusion at dose of $1\text{--}20\text{mcg/kg/hour}$ for short-term stabilization of glucose control in combination with octreotide in patients with hyperinsulinemic hypoglycemia. It activates adenylate cyclase via G-protein-coupled receptor thereby increasing glycogenolysis and gluconeogenesis [50]. Recent advances have shown the effectiveness of the mammalian target of rapamycin (mTOR) inhibitor, Sirolimus in infants with severe diffuse form of hyperinsulinemic hypoglycemia that had been unresponsive to maximal doses of diazoxide and octreotide [51]. Once glucose levels are stabilized, reduce and stop intravenous glucose infusion followed by glucagon and octreotide. The maintenance dose of octreotide is reduced in patients with severe hepatic impairment. These children with CHI are always at

increased risk of infection due to central line related sepsis and prolonged/multiple hospitalizations.

Molecular testing for mutations in genes responsible for CHI becomes necessary if hypoglycemia is diazoxide-unresponsive [52]. Confirmed cases of CHI should be differentiated into focal and diffuse forms using ¹⁸F-DOPA-PET scan to make surgical decision [53]. Laparoscopic excision is curative in focal forms whereas near total pancreatectomy is needed in diffuse disease [54]. Decision for surgery also includes dependence on high GIR requirement along with unresponsiveness to medications. In immediate post-operative period, some children may develop transient hyperglycemia needing insulin administration. Many children have persistent hypoglycemia following surgery needing on-going diazoxide therapy, before developing diabetes later on. Near total pancreatectomy leads to post-operative diabetes and exocrine pancreatic insufficiency in most of the infants

with diffuse persistent hyperinsulinemic hypoglycemia [55]. Infants on treatment for CHI should have long-term developmental follow up due to high risk of neurodevelopmental delay, cerebral palsy and epilepsy [35,36]. All the familial forms of CHI should undergo genetic counseling. **Fig. 2** suggests outline for the diagnosis and management of hyperinsulinemic hypoglycemia.

CONCLUSION

Being an important cause of hypoglycemia in infancy, early diagnosis and aggressive management of hyperinsulinemic hypoglycemia is the cornerstone for prevention of hypoglycemia induced neuronal injury. Molecular basis of the various forms of hyperinsulinemic hypoglycemia involving defects in key genes, which regulate insulin secretion, are beginning to be understood and being increasingly reported. One should keep in mind, the spectrum of clinical presentations of hyperinsulinemic

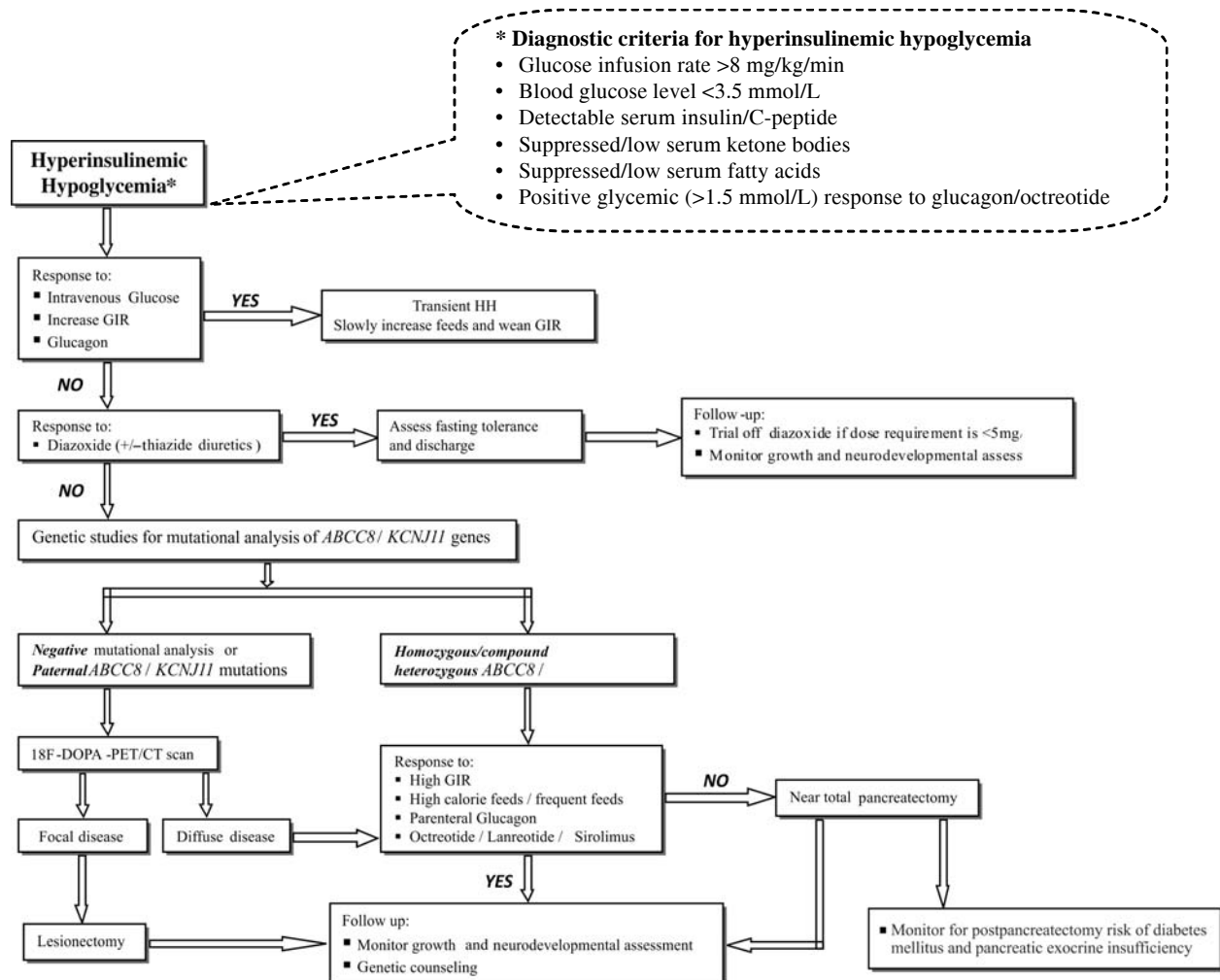


FIG. 2 Suggested outline for diagnosis and management of hyperinsulinemic hypoglycemia.

hypoglycemia. Diazoxide unresponsiveness in a baby with hyperinsulinemic hypoglycemia warrants genetic studies to look for common mutations and trials with newer drugs like lanreotide and sirolimus appears promising. However, the management of hyperinsulinemic hypoglycemia still remains a challenge to the neonatologists and endocrinologists, even in developed countries; due to lack of facilities for genetic studies and ¹⁸F-DOPA-PET scan. Novel insights in identifying genetic mechanisms in CHI will modify the futuristic approach to diagnosis and treatment of hyperinsulinemic hypoglycemia.

Contributors: SV: Literature search, manuscript drafting, review and editing; SC: Literature review and manuscript editing; VSR: Literature review and manuscript editing; KH: Guidance and final editing of manuscript with extensive literature search. All authors approved the final manuscript. SV will be the guarantor.

Funding: None; *Competing interest:* None stated.

REFERENCES

- Arya VB, Senniappan S, Guemes M, Hussain K. Neonatal hypoglycemia. *Indian J Pediatr.* 2014; 81:58-65.
- Straussman S, Levitsky LL. Neonatal hypoglycemia. *Curr Opin Endocrinol Diabetes Obes.* 2010;17:20-4.
- Menni F, de Lonlay P, Sevin C, Touati G, Peigne C, Barbier V, *et al.* Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics.* 2001;107:476-9.
- Hussain K, Blankenstein O, De Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management. *Arch Dis Child.* 2007;92:568-70.
- Hawdon J. Glucose homeostasis in the healthy fetus and neonate. *In: Rennie JM, editor. Metabolic and Endocrine Disorders. Textbook of Neonatology.* London: Elsevier, Churchill Livingstone. 2005;851-52.
- Henquin JC. Triggering and amplifying pathways of regulation of insulin secretion by glucose. *Diabetes.* 2000;49:1751-60.
- Yorifuji T. Congenital hyperinsulinism: Current status and future prospectives. *Ann Pediatr Endocrinol Metab.* 2014;19:57-68.
- Inagaki N, Gono T, Clement JP, Namba N, Inazawa J, Gonzalez G, *et al.* Reconstitution of IKATP: An inward rectifier subunit plus the sulfonylurea receptor. *Science.* 1995;270:1166-70.
- Zhang T, Li C. Mechanisms of amino acid-stimulated insulin secretion in congenital hyperinsulinism. *Acta Biochim Biophys Sin (Shanghai).* 2013;45:36-43.
- World Health Organization. Hypoglycaemia of the Newborn. Review of the Literature. Geneva: WHO, 1997;WHO/CHD/97.1.
- Thornton PS, Stanley CA, De Leon D, Harris D, Haymond MW, Hussain K, *et al.* Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr.* 2015; 167:238-45.
- Tin W. Defining neonatal hypoglycaemia: a continuing debate. *Semin Fetal Neonatal Med.* 2014;19:27-32.
- Adamkin DH, Committee on Fetus and Newborn. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127:575-79.
- Kapoor RR, Flanagan SE, James C, Shield J, Ellard S, Hussain K. Hyperinsulinaemic hypoglycaemia. *Arch Dis Child.* 2009;94:450-7.
- Vanhaltren K, Malhotra A. Characteristics of infants at risk of hypoglycaemia secondary to being 'infant of a diabetic mother'. *J Pediatr Endocrinol Metab.* 2013;26:861-5.
- Chong JH, Chandran S, Agarwal P, Rajadurai VS. Delayed presentation of prolonged hyperinsulinaemic hypoglycaemia in a preterm small-for-gestational age neonate. *BMJ Case Rep.* 2013. Doi:10.1136/bcr-2013-200920.
- Bellanne-Chantelot C, Saint-Martin C, Ribeiro MJ, Vaury C, Verkarre V, Arnoux JB, *et al.* ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. *J Med Genet.* 2010;47:752-59.
- James C, Kapoor RR, Ismail D, Hussain K. The genetic basis of congenital hyperinsulinism. *J Med Genet.* 2009;46:289-99.
- Mohammed Z, Hussain K. The genetics of hyperinsulinemic hypoglycemia. *NeoReviews.* 2013;14:179-88.
- Verkarre V, Fournet JC, de Lonlay P, Gross-Morand MS, Devillers M, Rahier J, *et al.* Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. *J Clin Invest.* 1998;102:1286-91.
- Flanagan SE, Clauin S, Bellanne-Chantelot C, de Lonlay P, Harries LW, Gloyn AL, *et al.* Update of mutations in the genes encoding the pancreatic b-cell K (ATP) channel subunits Kir6.2 (KCNJ11) and sulfonylurea receptor 1 (ABCC8) in diabetes mellitus and hyperinsulinism. *Hum Mutat.* 2009;30:170-80.
- Stanley CA, Lieu YK, Hsu BY, Burlina AB, Greenberg CR, Hopwood NJ, *et al.* Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med.* 1998;338:1352-7.
- MacMullen C, Fang J, Hsu BY, Kelly A, de Lonlay-Debeney P, Saudubray JM, *et al.* Hyperinsulinism/hyperammonemia syndrome in children with regulatory mutations in the inhibitory guanosine triphosphate-binding domain of glutamate dehydrogenase. *J Clin Endocrinol Metab.* 2001;86:1782-7.
- Hussain K, Clayton PT, Krywawych S, Chatziandreu I, Mills P, Ginbey DW, *et al.* Hyperinsulinism of infancy associated with a novel splice site mutation in the SCHAD gene. *J Pediatr.* 2005;146:706-8.
- Chandran S, Yap F, Hussain K. Molecular mechanisms of protein induced hyperinsulinaemic hypoglycaemia. *World J Diabetes.* 2014;5:666-77.
- Cuesta-Muñoz A, Huopio H, Otonkoski T, Gomez-Zumaguer JM, Nantö-Salonen K, Rahier J, *et al.* Severe persistent hyperinsulinemic hypoglycemia due to a de novo glucokinase mutation. *Diabetes.* 2004;53:2164-8.

27. Gonzalez Barroso MM, Giurgea I, Bouillaud F, Anedda A, Bellanne Chantelot C, Hubert L, *et al.* Mutations in UCP2 in congenital hyperinsulinism reveal a role for regulation of insulin secretion. *PLoS One*. 2008;3:e3850.
28. Gupta RK, Vatamaniuk MZ, Lee CS, Flaschen RC, Fulmer JT, Matschinsky FM, *et al.* The MODY1 gene HNF 4alpha regulates selected genes involved in insulin secretion. *J Clin Invest*. 2005;115:1006-15.
29. Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, *et al.* Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med*. 2007;4:e118.
30. Otonkoski T, Kaminen N, Ustinov J, Lapatto R, Meissner T, Mayatepek E, *et al.* Physical exercise-induced hyperinsulinemic hypoglycemia is an autosomal-dominant trait characterized by abnormal pyruvate induced insulin release. *Diabetes*. 2003;52:199-204.
31. Munns CF, Batch JA. Hyperinsulinism and Beckwith-Wiedemann syndrome. *Arch Dis Child Fetal Neonatal Ed*. 2001;84:F67-9.
32. Sun L, Eklund EA, Chung WK, Wang C, Cohen J, Freeze HH. Congenital disorder of glycosylation id presenting with hyperinsulinemic hypoglycemia and islet cell hyperplasia. *J Clin Endocrinol Metab*. 2005;90:4371-5.
33. Baumann U, Preece MA, Green A, Kelly DA, McKiernan PJ. Hyperinsulinism in tyrosinaemia type I. *J Inherit Metab Dis*. 2005;28:131-35.
34. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *Eur J Endocrinol*. 2013;168:557-64.
35. Vannucci RC, Vannucci SJ. Hypoglycemic brain injury. *Semin Neonatol*. 2001;6:147-55.
36. Chandran S, Rajadurai VS, Alim AH, Hussain K. Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk. *Research and Reports in Neonatology*. 2015;5:17-30.
37. Mazor-Aronovitch K, Gillis D, Lobel D, Hirsch HJ, Pinhas-Hamiel O, Modan-Moses D, *et al.* Long-term neurodevelopmental outcome in conservatively treated congenital hyperinsulinism. *Eur J Endocrinol*. 2007;157:491-7.
38. Wang L, Fan G, Ji X, Sun B, Guo Q. MRI findings of brain damage due to neonatal hypoglycemia. *Zhonghua Fang She Xue Za Zhi*. 2009;43:42-5.
39. Deshpande S, Ward Platt M. The investigation and management of neo-natal hypoglycaemia. *Semin Fetal Neonatal Med*. 2005;10:351-61.
40. Senniappan S, Arya VB, Hussain K. The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. *Indian J Endocr Metab*. 2013;17:19-30.
41. Harris DL, Battin MR, Weston PJ, Harding JE. Continuous glucose monitoring in newborn babies at risk of hypoglycemia. *J Pediatr*. 2010;157:198-202.
42. Saif M, Kapoor A, Kochar IP, Jindal R. Continuous glucose monitoring system for congenital hyperinsulinemia. *Indian Pediatr*. 2013;50:421-2.
43. Hussain K. Investigations for neonatal hypoglycaemia. *Clin Biochem*. 2011;44:465-6.
44. Hussain K, Blankenstein O, De Lonlay P, Christesen HT. Hyperinsulinaemic hypoglycaemia: biochemical basis and the importance of maintaining normoglycaemia during management. *Arch Dis Child*. 2007;92:568-70.
45. Aynsley-Green A, Hussain K, Hall J, Saudubray JM, Nihoul-Fékété C, De Lonlay-Debeney P, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed*. 2000;82:F98-107.
46. Tas E, Mahmood B, Garibaldi L, Sperling M. Liver injury may increase the risk of diazoxide toxicity: a case report. *Eur J Pediatr*. 2015;174:403-6.
47. Hussain K. Diagnosis and management of hyperinsulinaemic hypoglycaemia of infancy. *Horm Res*. 2008;69:2-13.
48. Kim-Hanh Le Quan Sang, Jean-Baptiste Arnoux, Asmaa Mamoune, Saint-Martin C, Bellanné-Chantelot C, Valayannopoulos, *et al.* Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur J Endocrinol*. 2012;166:333-9.
49. Modan-Moses D, Koren I, Mazor-Aronovitch K, Pinhas-Hamiel O, Landau H. Treatment of congenital hyperinsulinism with Lanreotide acetate (Somatuline Autogel). *J Clin Endocrinol Metab*. 2011; 96:2312-7.
50. Moens K, Berger V, Ahn JM, Van Schravendijk C, Hruby VJ, Pipeleers D, *et al.* Assessment of the role of interstitial glucagon in the acute glucose secretory responsiveness of in situ pancreatic beta-cells. *Diabetes*. 2002;51:669-75.
51. Senniappan S, Alexandrescu S, Tatevian N, Shah P, Arya V, Flanagan S, *et al.* Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. *N Engl J Med*. 2014;370:1131-7.
52. Hussain K, Aynsley-Green A. Hyperinsulinaemic hypoglycaemia in preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2004;89:F65-7.
53. Mohnike K, Blankenstein O, Christesen HT, de Lonlay J, Hussain K, Koopmans KP, *et al.* Proposal for a standardized protocol for 18-F DOPA-PET (PET/CT) in congenital hyperinsulinism. *Horm Res*. 2006;66:40-2.
54. Bax KN, van der Zee DC. The laparoscopic approach towards hyperinsulinism in children. *Sem Ped Surg*. 2007;16:245-51.
55. Leibowitz G, Glaser B, Higazi AA, Salameh M, Cerasi E, Landau H. Hyperinsulinemic hypoglycemia of infancy (nesidioblastosis) in clinical remission: High incidence of diabetes mellitus and persistent beta-cell dysfunction at long-term follow-up. *J Clin Endocrinol Metab*. 1995;80:386-92.