Review

Hyperinsulinemic Hypoglycemia in Childhood

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ABSTRACT

Hyperinsulinemic Hypoglycemia (HH) is the most common cause of permanent hypoglycemia, especially in the neonatal period. Childhood HH is mostly related to genes encoding proteins in the insulin secretion pathways, and may also be seen in syndromes such as Beckwidth Wiedemann, Kabuki, and Turner. The majority of congenital HH cases are the result of KATP channel gene defect. Most of these cases are unresponsive to diazoxide treatment. In this review, recent genetic studies and recent updates in treatment options in childhood HH are reviewed.

Keywords: Hyperinsulinemic Hypoglycemia, Childhood, KATP gene, Diazoxide, Octreotide

INRODUCTION

Hyperinsulinemic Hypoglycemia (HH) is the most common cause of severe and persistent hypoglycemia resulting from impaired suppression of insulin secretion from pancreatic beta cells. The presence of measurable insulin in the blood sample taken when blood glucose is <50 mg/dl, along with low free fatty acid level and low blood ketone value, make the diagnosis of HH [1,2]. Insulin has a plasma life of 6 minutes and is secreted pulsatilely. For this reason, insulin may not be measured high in HH cases sometimes. The serum C-peptide level is more stable and has a 24-hour lifespan. It is a more reliable parameter for the diagnosis of HH than insulin [2,3]. In addition, the need for >6-8 mg/kg/min dextrose infusion to ensure normoglycemia and a positive response to glucagon injection support the diagnosis of HH. The development of hypoglycemia after protein intake or after exercise in older children should also bring HH to mind. Depending on the age group, hypoglycemia may cause adrenergic symptoms such as feeding problem, hypotonia, feeling of hunger, weakness, sweating, palpitation, and nervousness. As the severity of hypoglycemia increases, neuroglycopenic findings,

convulsions, loss of consciousness and permanent neurological sequelae, and even death may occur due to the inability to meet the glucose requirement of the brain. Babies with HH are usually macrosomic, and some of them may have cardiomyopathy and hepatomegaly due to glycogen storage [1-3].

Insulin is the main regulator of blood sugar. It increases the use of blood sugar by providing the passage of cells. At the same time, it increases the storage of glycogen in the liver and muscles, while suppressing endogenous glucose production pathways such as gluconeogenesis and glycogenolysis. Insulin also inhibits lipolysis in adipose tissue and suppresses ketone formation.

Glucose, which increases in the blood after meals, enters the pancreatic beta cell via GLUT-2. It is converted to glucose-6-phosphate (G6P) by the enzyme glucokinase (GCK). As glucose 6 phosphate is metabolized by glycolysis, energy (ATP) is released. When the ATP/ADP ratio increases, ATP-sensitive potassium channels (KATP) are closed. These channels consist

of two proteins called sulfonylurea receptor 1 (SUR1) and Kir6.2 (Inward rectifier potassium channel) encoded by ABCC8 and KCNJ11 genes. It is normally responsible for potassium flow out of the cell. With the closure of the KATP channel, a membrane potential (depolarization) occurs in the beta cell. Voltage sensitive calcium channels open due to the membrane potential formed between the inside and outside of the cell. Calcium flows into the cell. Increased intracellular calcium causes cytosolic contractions in insulin-stored granules and insulin release by exocytosis (Figure 1).
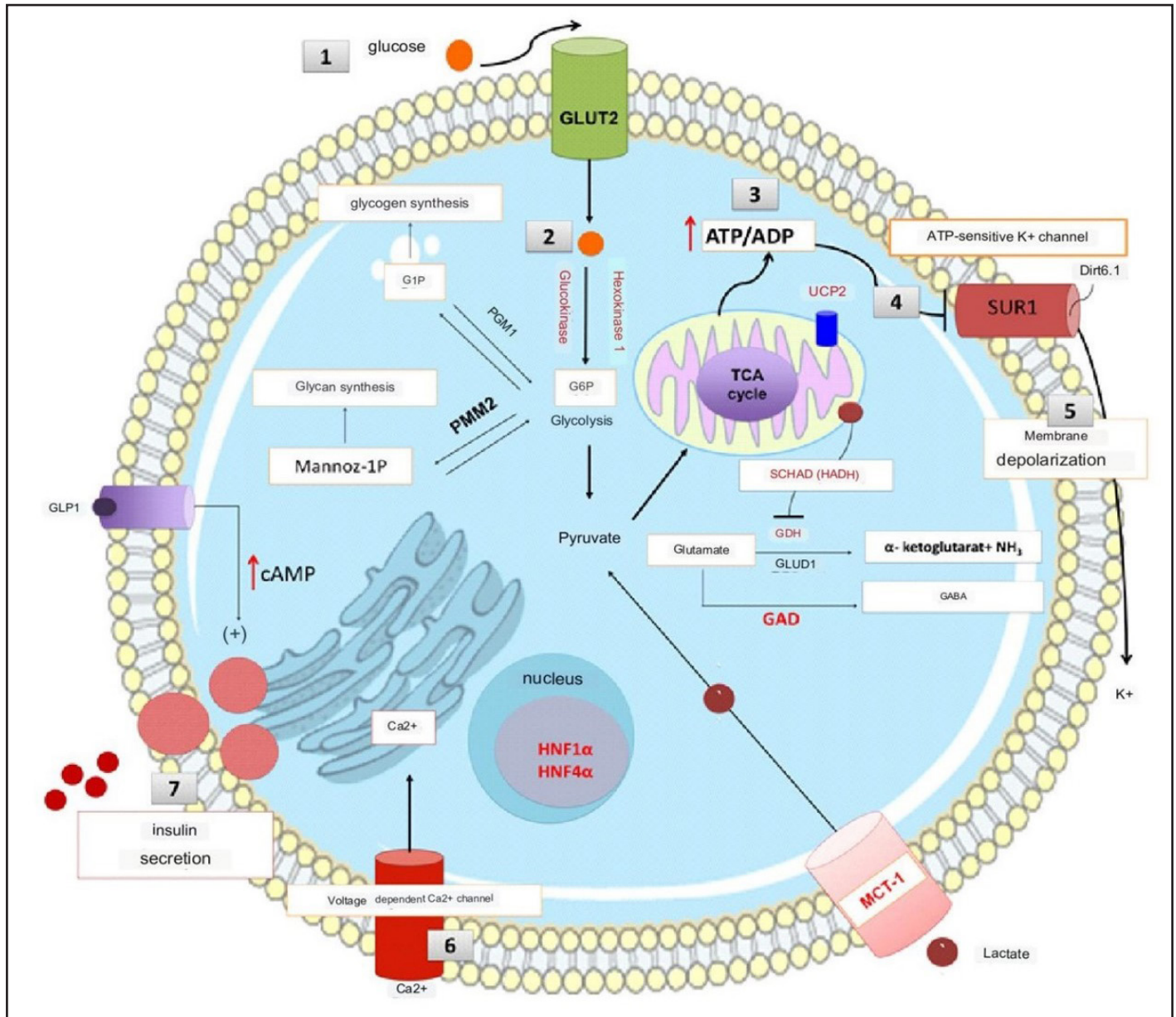
Figure 1. Regulation of insulin release from pancreatic β-cell and sites of gene mutations involved in the genetics etiology of hyperinsulinaemic hypoglycaemia

SUR1: sulphonlyurea receptor 1, **Kir6.2:** inwardly rectifying potassium channel 6.2, **K:** potassium, **MCT1:** monocarboxylate transporter 1, **Glu:** glucose, **P:** phosphorus; **PGM1:** phosphoglucomutase 1, **PMM2:** phosphomannose-mutase 2, **UCP2:** mitochondrial uncoupling protein 2, **NH3:** ammonia, **GDH:** glutamate dehydrogenase, **GLUD1:** glutamate dehydrogenase 1 gene, **SCHAD:** short-chain L-3-hydroxyacyl-CoA dehydrogenase, **HADH:** hydroxy-acyl-CoA dehydrogenase, **HNF1A and 4A:** hepatocyte nuclear factor 1A and 4A, **Ca+2:** calcium; **GAD:** glutamate decarboxylase enzyme, **GABA:** γ-aminobutyric acid, **GLP1:** glucagon like peptide 1, **cAMP:** cyclic adenosine monophosphate (amplifier for the exocytosis of insulin secreting granule. [1].

Insulin has a blood sugar lowering effect. In normal situations, when blood sugar begins to fall below the threshold value (85-90 mg/dl in plasma), insulin secretion begins to decrease, and when it falls below 50 mg/dl, insulin secretion must decrease to undetectable levels. All kinds of events that affect the functioning of this cycle, which plays a role in the release of insulin from β-cells, cause severe hypoglycemia, as a result of which insulin secretion cannot be suppressed. For these reasons, if normoglycemia (> 60 mg/dl) cannot be achieved in 6-8 hours of fasting, especially in newborns after 48-72 hours, permanent hypoglycemia should be mentioned and its cause should be investigated [4,5].

Hyperinsulinemic Hypoglycemia

In particular, HH of genetic origin is usually seen in newborns, but it can also be seen in infancy or older ages. Patients who are protein sensitive and develop hypoglycemia after exercise show clinical signs in later months. Hyperinsulinemic Hypoglycemia due to insulinoma can present clinically at any age, including adult age.

Hyperinsulinemic Hypoglycemia can be temporary or permanent, sometimes accompanied by syndromes. Temporary HH can be seen in the baby of diabetic mother, Rh incompatibility, erythroblastosis fetalis, intrauterine growth retardation, SGA, drugs such as propronalol, sulfonylurea taken by the mother, or hyperglycemia due to stress in the mother. The main mechanism in these cases is transient hyperinsulinism. They usually resolve spontaneously within the first 1-2 months, rarely, hyperinsulinemia may persist for more than 6 months [6]. Hyperinsulinemic Hypoglycemia can be seen together with various syndromes. Hyperinsulinemic Hypoglycemia has been reported in syndromic channelopathies such as overgrowth syndromes (such as Beckwith-Wiedemann syndrome (BWS) and Sotos syndrome), monogenic or chromosomal developmental syndromes with postnatal growth retardation (Turner syndrome, Kabuki syndrome, etc.), congenital glycosylation syndromes and Timoty syndrome [7].

Beckwith-Wiedemann syndrome is the most common cause of HH. BWS is a type of overgrowth syndrome that includes macrosomia, macroglossia, neonatal hypoglycemia, hemi-hypertrophy, and omphalocele. Patients with BWS are predisposed to develop embryonal malignancies such as Wilms' tumor, hepatoblastoma, neuroblastoma, and rhabdomyosarcoma.

Hyperinsulinemic Hypoglycemia develops in around 50% of BWS patients and is usually transitory. However, in some circumstances, it may produce HH that is resistant to diazoxide and, in rare cases, may necessitate pancreatectomy [8]. In certain BWS patients, HH may be the primary clinical finding, with no other symptoms of the disease [9]. Beckwith-Wiedemann syndrome is caused by genetic and/or epigenetic defects that alter the expression of imprinting genes on chromosome 11's short arm (11p15.5) [10]. The presence of the KATP gene on the short arm of the 11th chromosome appears to facilitate the onset of hyperinsulinism [7].

Kabuki Make Up syndrome has been reported as the second most common syndrome causing HH in some series. Kabuki syndrome is a rare hereditary multisystem disorder marked by developmental delays, large palpebral fissures, lateral epicanthus, permanent fingertip pads and dermatoglyphic abnormalities, as well as several congenital skeletal and visceral malformations. Kabuki syndrome has been linked to mutations on the X chromosome in the KMT2D (75%) and KDM6A (3-5%) genes. Both genes encode proteins that regulate histones, so they are in the group of chromatin regulation disorders [7]. Especially in Kabuki syndrome due to KMD6A gene mutation, 56% of neonatal hypoglycemia and 28% of HH can be found to affect the β-cell function of this gene, but the exact mechanism is not clear yet [11]. The HH seen in Kabuki syndrome responds to diazoxide and usually resolves within the first 2 years. However, cases in which pancreatectomy had to be performed have also been reported [12].

Turner syndrome is a relatively common (1/2500 female birth) syndrome, characterized by short stature and ovarian insufficiency. The association of cases with Turner syndrome and HH has been reported, and when the cases in some series are evaluated, it has been predicted that HH is seen 50 times more often than the normal population [7]. Moreover, in a study in which HH was found in 9 out of 69 patients with Turner syndrome, they stated Turner syndrome as the third most common syndrome in which HH was detected [12]. In cases of Turner syndrome, KDM6A "haploinsufficiency" induced by mosaic X chromosome monosomy was assumed to be the etiology of HH. Most of the cases are responsive to diazoxide, and the need for medication usually disappears within 1 year, but cases that went to pancreatectomy have also been reported [7].

Tablo 1. Etiology of Hyperinsulinemic Hypoglisemia in Childhood [2,3]

Transient hyperinsulinaemic hypoglycaemia
• Mother with diabetes (before and during gestation)
• Maternal use of sulfonylureas or intrapartum intravenous glucose infusion
• Intrauterine growth restriction
• Perinatal asphyxia
• Rhesus haemolytic disease
• Erythroblastosis fetalis
• HNF4A, HNF1A mutation
Persistent hyperinsulinaemic hypoglycaemia

• Congenital hyperinsulinism (genetic hyperinsulinaemic hypoglycaemia
    ABCC8, KCNJ11,
    KCNQ1, CACNA1D, SLC16A1,
    GLUD1,
    GCK,
    HADH,
    HNF4A, HNF1A
    FOXA2
    EIF2S3
    UCP2
    HK1

• Insulinoma
Syndromic or metabolic causes of hyperinsulinism

Prenatal and postnatal overgrowth syndromes:
    • Beckwith-Wiedemann syndrome
    • Soto's syndrome
    • Simpson-Golabi-Behmel syndrome
    • Perlman syndrome
Chromosomal abnormality syndromes:
    • Trisomy 13 (Patau syndrome)
    • Mosaic Turner syndrome

Contiguous gene deletion affecting the ABCC8 gene:
    • Usher syndrome
Syndromes leading to abnormalities in calcium homoeostasis:
    • Timothy syndrome

Insulin receptor mutation:
• Insulin resistance syndrome (leprechaunism)
Congenital disorders of glycosylation
• Types 1a, 1b, and 1d (PMM2, PGM1)

HNF1A: Hepatocyte nuclear factor 1A; **HNF4A:** Hepatocyte nuclear factor 4A; **ABCC8:** ATP Binding Cassette Subfamily C Member 8; **KCNJ11:** Potassium Voltage-Gated Channel Subfamily J Member 1; **KCNQ1:** Potassium Voltage-Gated Channel Subfamily Q Member 1; **CACNA1D:** Calcium Voltage-Gated Channel Subunit Alpha1 D; **SLC16A1:** solute carrier family 16 member; **GLUD1:** glutamate dehydrogenase 1; **HADH:** hydroxyacyl-CoA dehydrogenase; **GCK:** glucokinase; **UCP2:** uncoupling protein 2; **HK1:** hexokinase 1; **PGM1:** phosphoglucomutase 1; **PMM2:** phosphomannomutase 2, **FOXA2:** forkhead box protein A2; **EIF2S3:** Eukaryotic translation initiation factor 2 subunit 3.

Genetic Basis of Persistent Hyperinsulinemic Hypoglycemia

Persistent HH is mostly due to genes encoding pancreatic β-cell membrane ion channels and carrier proteins (ABCC8, KCNJ11, KCNQ1, SLC16A1, CACNA1D), enzymes in glucose metabolic pathways (GLUD1, GCK, HADH, UCD2, HK1, PMM2, PGM1) and transcription factors in insulin production (HNF4A, HNF1A, FOXA2). To date, mutations in nearly 15 genes, some of which have been presented as a single case, have been shown to cause HH [1-3]. In Table 1, the genes detected in HH cases are given as a table [3]. However, in approximately half of the cases, a genetic cause cannot be demonstrated [1].

Recessive loss-of-function mutations in KCNJ11 and ABCC8 genes, which encode two major proteins of the KATP channel, Kir6.2 and SUR1, are the most common cause of CHI (Congenital hyperinsulinism). Mutations in ABCC8 and KCNJ11 genes are responsible for approximately half of CHI cases [2]. ABCC8 gene mutations encoding the SUR1 protein constitute the majority of these in our country [13]. ABCC8/KCNJ11 recessive inactivating mutations are mutations that completely disrupt the synthesis of KATP channel proteins, thus channel formation and activity (class I) or reduce channel activity (class II), so cause uncontrolled insulin release despite severe hypoglycemia [14]. Mutations in these genes are also the most common cause of diffuse β-cell hyperplasia unresponsive to medical therapy [15]. Again, paternally inherited recessive mutations of KATP channel genes cause HH due to focal β-cell hyperplasia as a result of somatic mutation in pancreatic islet cells and loss of maternal allele (Paternal uniparental disomy, UPD). Dominant inactivating ABCC8 and KCNJ11 mutations usually cause milder phenotype HH, although cases unresponsive to medical treatment have also been reported [16].

KCNQ1 gene mutations cause cardiac arrhythmia (hereditary long QT syndrome), deafness, and gastrointestinal system disorders. Recently, HH has been reported in individuals with hereditary long QT syndrome caused by KCNQ1 mutations [17]. In these patients, uncontrolled insulin release and hypoglycemic episodes are seen later in the test during the long oral glucose

tolerance test. Although the role of Kv7.1 channels encoded by the KCNQ1 gene in glucose metabolism has not been fully explained, it has been suggested that this channel may regulate insulin secretion by playing a role in the repolarization of the plasma membrane.

The "Calcium Voltage-Gated Channel Subunit Alpha1 D (CACNA1D)" gene encodes L-type voltage-sensitive calcium channels, and mutations in this gene affect insulin secretion in pancreatic β-cells. Recently, the CACNA1D mutation was demonstrated in a patient with HH, cardiac disorders and severe hypotonia. This mutation activates L-type voltage-dependent Ca2+ channels, causing the channel to remain open even at lower membrane potential, causing uncontrolled calcium entry into the cell and insulin secretion [18].

Monocarboxylate carrier protein 1 (MCT1) are carrier proteins that allow monocarboxylate molecules such as lactate and pyruvate to be taken into the cell, and from there, pyruvate to be transported into the mitochondria and enter the "Kreb's cycle". The MCT1 protein is encoded by the SLC16A1 gene. Under normal conditions, the expression of the MCT1 protein in the β-cell is low. This results in low lactate-pyruvate levels in the β-cell and minimal effect on insulin secretion. Activating dominant mutations in the promoter region of the SLC16A1 gene cause MCT1 expression in the β-cell, lactate and pyruvate uptake into the cell, and pyruvate entering the Krebs' cycle, resulting in increased ATP synthesis and thus uncontrolled insulin secretion [19]. This form of HH, defined as exercise-induced hyperinsulinism, is characterized by autosomal dominant inheritance, inappropriate insulin secretion after anaerobic exercise and pyruvate loading. In these cases, which usually respond to diazoxide treatment, it is usually sufficient to avoid heavy exercises and there is no need for a continuous drug treatment. However, in some cases, diazoxide alone cannot prevent hypoglycemia, and it may be necessary to avoid heavy anaerobic exercise and to take carbohydrate-containing foods before, during and/or after exercise [20].

The Glutamate Dehydrogenase 1 (GLUD1) gene catalyzes the synthesis of α-ketoglutarate, a substrate for the Krebs cycle, in pancreatic β-cells. Thus, it causes an increase in the ratio of ATP: ADP, which activates the KATP channel in the cell, depolarization of the cell membrane and increase in exocytosis insulin secretion. GDH also catalyzes the deamination of L-glutamate and its conversion to α-ketoglutarate and ammonia

in the liver and kidney. Activating GLUD1 mutations have been reported as the second most common cause of HH [1]. GLUD1 mutations cause protein/leucine-induced hyperinsulinism/hyperamonemia syndrome (HI/HA) [21]. In these patients, 3-5 times higher ammonia level is observed due to increased ammonia production in the kidneys. It does not cause ammonia toxicity symptoms such as hyperammonemia, drowsiness, headache, vomiting, coma in these patients. However, epileptic seizures may be seen in some patients with mutations, especially in the 6th and 7th exons. Since these seizures can occur without hypoglycemia, it is thought that the mutation may have a direct effect on the brain [22]. Since HI/HA syndrome generally has a milder clinical course compared to KATP gene mutations, the diagnosis can be made after the neonatal period. In normal birth weight infants, persistent but asymptomatic hyperammonemia is characterized by fasting or postprandial protein/leucine-induced hypoglycemia. Neurological findings such as epilepsy and learning difficulties are more common in patients with HI/HA syndrome than other causes of hyperinsulinism.

Recessive inactivating mutations of the HADH gene cause a decrease in mitochondrial L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH) enzyme levels, and the inhibitory effect on GDH is lost, thus causing HH. In HADH deficiency, HADH gene mutations make protein sensitive HH. However, since the increase in GDH activity is limited to pancreatic islets, the increase in ammonia level seen in cases with HI/HA syndrome is not seen here. Patients may present with a heterogeneous clinical picture ranging from mild or late-onset, fasting or protein/leucine-sensitive hypoglycemia to severe hypoglycemia immediately after birth [23,24]. Congenital hyperinsulinism due to HADH gene mutations almost always responds to diazoxide treatment. However, in order to prevent protein-induced HH in these patients, patients should also be advised to avoid meals containing pure protein.

The glucokinase enzyme encoded by the GCK gene is a hexokinase (Hexokinase IV) that phosphorylates the glucose entering the beta cell to form G6P. This enzymatic reaction constitutes the rate limiting step for glycolysis. Because of this feature, it plays a glucosensor role for glucose-stimulated insulin secretion from the β-cell. Heterozygous (dominant) activating mutations in the GCK gene increase the enzyme's affinity for glucose. Enzyme activity continues even at low glucose levels, thereby increasing ATP production. The increased ATP/ADP ratio causes the KATP channels in the pancreatic β-cell

membrane to remain closed for a long time and uncontrolled insulin release. Activating heterozygous mutations in the GCK gene cause HH with autosomal dominant inheritance [25]. The onset of the disease may occur in a wide age range from the neonatal period to the adulthood [26]. The severity of clinical findings varies among affected individuals. There is usually a family history of hypoglycemia. However, since the severity of the disease may be different in affected individuals, the picture may be quieter in previous individuals. Affected individuals may even become ill without being aware of it [27]. Although most GCK mutations lead to HH that responds to diazoxide therapy, some patients may need octreotide administration or pancreatectomy [26].

In addition to GDH1, HADH and GCK, which are found in the metabolic pathways of glucose, HH is also seen due to uncoupling 2, (UCP2), Hexokinase 1 (HK1), and PGM1 and PMM2 gene mutations that cause congenital glycation disorders. Theoretically, this group of patients is expected to be responsive to diazoxide, since the KATP channel proteins are intact.

Hepatocyte nuclear factor 1α and 4α (HNF1α and HNF4α), which act as transcription factors for nuclear hormone receptors encoded by the HNF1A and HNF4A genes, are also expressed in β-cells that regulate insulin secretion. Heterozygous inactivating mutations of these genes cause two contrasting clinical pictures; While they cause HH in newborns and infants, they cause MODY type diabetes (MODY type 1 and 3), which is called early-onset monogenic diabetes in the later stages of life. Hyperinsulinemic Hypoglycemia patients due to HNF1A/HNF4A mutations are typically macrosomic and may cause disease in a clinical spectrum ranging from mild transient hypoglycemia to severe HH responsive to diazoxide [28,29]. Although HH due to HNF1A and HNF4A mutations is rare, it has been reported as one of the most common causes of diazoxide-sensitive HH in some series [29].

Cases of HH due to Forkhead box A2 transcription factor (FOXA2), also known as hepatocyte nuclear factor 3β (HNF3β), have been reported. The FOXA2 gene is one of the positive regulators of the pdx1 gene, which has a role in pancreatic development [30]. The FOXA2 gene is also involved in the expression of KCNJ11 and ABCC8. On the other hand, it has been reported that the FOXA2 gene is a binding point in the intronic region of the HADH gene and plays a role in the activation of the HADH gene. The first FOXA2 mutation, which

causes pituitary dysfunction and clinical findings accompanied by HH, was shown in a patient with congenital hypopituitarism, HH, and organ anomalies differentiated from the endoderm [31].

Histopathology in Hyperinsulinemic Hypoglycemia
Congenital HH is histologically divided into two subgroups as diffuse and focal disease. The diffuse form is typically characterized by enlargement and hyperplasia of β-cells. In the focal form, there is nodular hyperplasia consisting of ductal and acinar complexes surrounded by normal pancreatic tissue. The diffuse form cases, which constitute 40-50% of the cases, are usually seen due to recessive or dominant inherited ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A and UCP2 gene mutations. Focal forms generally develop as a result of paternal unidisomy, loss of maternal 11p15 somatic allele and ABCC8/KCNJ11 gene mutation [2].

It is possible to distinguish between diffuse and focal forms with ^{18}F-DOPA-PET/CT imaging. This provides us a chance of surgical cure, especially in focal forms [32].

Treatment and Management in Hyperinsulinemic Hypoglycemia
The primary goal in the treatment of HH is to bring blood sugar to the normoglycemic level as soon as possible, and to allow sufficient ketone production if possible [1,2]. Because glucose and ketone bodies are the main and alternative energy sources of the brain. Since lipolysis is suppressed at high insulin levels, ketone production is also suppressed, thus increasing the risk of brain damage and sequelae [33,34]. For this reason, it should be aimed to increase blood sugar to at least 60-65 mg/dl and above, which is the safe range, and to control inappropriate insulin secretion.

Emergency Treatment of Hyperinsulinemic Hypoglycemia
When hypoglycemia is detected, after critical blood samples are taken, solutions containing 0.2 mg/kg glucose (2 cc/kg 10% dextrose) are injected intravenously to bring blood sugar back to normal as soon as possible. Blood glucose is measured within 5-10 minutes after the first bolus, and a bolus is given again if necessary. If it still does not improve, higher doses and repeated pushes are applied. On the other hand, even if normoglycemia is achieved, fluid containing dextrose is started with a glucose infusion rate of 6-8 mg/kg/min and above. The amount of dextrose in the fluid and the glucose infusion rate are titrated according to the blood glucose level obtained in

repeated measurements. An important point to note here is that bolus dextrose push-ups stimulate insulin release and there is a risk of rebound hypoglycemia. For this reason, it is appropriate to avoid boluses whenever possible and to start dextrose fluid infusion immediately after the first push if intravenous dextrose is needed.

Intramuscular glucagon can be life-saving in cases such as symptomatic hypoglycemia, hypoglycemic seizures, or patients with vascular access issues by boosting blood sugar within minutes. Each injection should have a dose of 0.5-1 mg [1,2]. While glucagon primarily raises blood sugar through glycogenolysis in the liver, it also creates an immediate energy source for brain tissue by stimulating gluconeogenesis, ketogenesis, and lipolysis [35].

Frequent feeding of the patient according to the fasting tolerance period may also help for normoglycemia. However, severe anorexia usually occurs in HH patients, especially with the effect of diazoxide treatment. Another important problem is vomiting and gastroesophageal reflux, which are frequently seen in these patients. Antireflux treatment for gastroesophageal reflux, percutaneous gastrostomy and, in some cases, antireflux surgery may be required [36]. On the other hand, while switching to oral nutrition, insulin secretagogues secreted from the gastrointestinal tract may increase hypoglycemia and intravenous glucose requirement in these patients.

Long-term Treatment
Medical treatment
The mechanism of action and possible side effects of drugs used in the treatment of HH are summarized in the table 2. Diazoxide is a potent inhibitor of insulin secretion and is the first-line drug of medical treatment in HH [1-3]. Diazoxide binds to the KATP channel SUR1 subunit, thereby inhibiting insulin secretion by channel's opening and showing its activity. Most of the cases of diffuse HH caused by homozygous or compound heterozygous mutations in ABCC8 and KCNJ11 genes in which the KATP channel structure and/or function is impaired, and focal HH caused by paternally inherited heterozygous mutations of the same genes are unresponsive to diazoxide. If normoglycemia is still not achieved at a dose of 15 mg/kg/day for 5 days, it is considered unresponsive to diazoxide. The most common acute side effect is fluid and salt retention. Water retention is more common in newborns and infants and may cause congestive heart failure [1,37]. It is frequently used in combination with

chlorothiazide (7-10 mg/kg/day and in 2 divided doses), a thiazide diuretic, to protect against fluid retention and have a synergistic effect against hyperinsulinism. However, there is no need to routinely start chlorothiazide in patients who do not have clinical signs of fluid retention, except in the newborn and infancy period.

Although nifedipine, a calcium channel blocker, is a promising molecule due to the role of voltage-dependent calcium channels in the insulin release mechanism from beta cells, its success in CHI treatment in clinical practice has been limited [38,39].

Octreotide is accepted as the second alternative drug after diazoxide in HH. By binding to somatostatin receptors 2 and 5 (SSTR2 and SSTR5), it provides a potent inhibitory effect on insulin release from pancreatic beta cells. The recommended starting dose for octreotide is 5 µg/kg/day administered subcutaneously, given in 4-6 divided doses. The maximum treatment dose is accepted as 35-40 µg/kg/day [1-3].

In patients who cannot achieve normoglycemia with conventional treatments, surgical pancreatectomy is required. In some cases, normoglycemia was achieved with Sirolimus, an mTOR inhibitor, before surgery and the need for pancreatectomy was eliminated. The treatment dose is started in two equally divided doses at a dose of 0.5-1 mg/m2/day and titrated with the weekly sirolimus level. Sirolimus blood level is targeted as 5-15 ng/mL [40]. Due to its serious side effects, sirolimus is still recommended to be used as the last option of medical therapy in the treatment of HH. In addition, it was reported that the chance of success with sirolimus was not as expected in HH series that included a small number of diazoxide-resistant patients [41,42]. Long-acting somatostatin analogs (Octreotide/Lanreotide LAR) are a new treatment option administered deep intramuscularly every 28 days. Especially in chronic treatment, it is a candidate to be the first choice for patients who have compliance problems in daily use of diazoxide and octreotide. It has similar side effects to short-acting octreotide. It appears to be more effective than conventional treatments [2].

Surgical Approach
If normoglycemia cannot be achieved with current treatments in HH, surgical pancreatectomy should be planned. In cases of diffuse HH unresponsive to treatments, >95% of the pancreas is removed. If a focal lesion is detected, cure is achieved by removing only the focal lesion [1,2]. In a study including 105

cases with 58 diffuse and 47 focal lesions who underwent surgery; diffuse cases underwent near-total pancreatectomy, hyperglycemia was observed in 53% of cases, and 10 required a second operation, and the need for postoperative medical treatment continued in 59%, but this need was reported to have passed within 5 years. No post-operative hyperglycemia developed in focal patients and all were cured. In the same study, 91% of diffuse HH patients who underwent near-total pancreatectomy developed diabetes requiring insulin in their 14th year [32].

Tablo 2. Medications for the treatment of hyperinsulinaemic hypoglycemia [1]

	Route	Dose	Mode of action	Side effects
Conventional Medicines				
Diazoxide	Oral	5-20 mg/kg/day, divided into three doses	Binds to the SUR1 subunit of KATP channels, opening them and inhibiting insulin secretion. To function effectively, the KATP channel must be intact.	Water and salt retention, hypertrichosis, and loss of appetite are all common symptoms. Cardiac failure, pulmonary hypertension, hyperuricaemia, blood dyscrasias (bone marrow suppression, anaemia, eosinophilia, etc.), and paradoxical hypoglycemia are uncommon.
Chlorothiazide	Oral	7-10 mg/kg/day, divided into two doses	Prevents fluid retention and has a synergistic impact on KATP channels with diazoxide to reduce insulin secretion.	Hyponatraemia, hypokalaemia
Nifedipine	Oral	0.25-2.5 mg/kg/day in 2-3 split doses	Inhibits Ca-channels of the β-cell membrane Ca-channels in the -cell membrane are inhibited.	Hypotension
Octreotide	s.c	5-35 g/kg/day, split into 3-4 doses or administered as a continuous subcutaneous infusion	SSTR2 and SSTR5 activation limits calcium mobilization and cholinergic activity, decreases insulin gene promoter activity, and decreases insulin production and release.	Acute symptoms include anorexia, nausea, abdominal pain, diarrhoea, drug-induced hepatitis, increased liver enzymes, long QT syndrome, tachyphylaxis, and necrotizing enterocolitis. Long-term effects include decreased intestinal motility, bile sludge, and gallstone formation, as well as suppression of pituitary hormones (growth hormone, TSH).
Glucagon	bolus s.c/i.m or infusion s.c/i.v	0.02 mg/kg dosage or infusion rate of 5-10 g/kg/hour	G-protein-coupled adenylate cyclase activity raises cAMP. Glycogenolysis and gluconeogenesis are stimulated.	High doses (>20 g/kg/hour) cause nausea, vomiting, skin rash, and rebound hypoglycemia due to paradoxical stimulation of insulin secretion.
New medicines				
Rapamycin (everolimus, sirolimus)	Oral	An initial dose of 1 mg/m2 per day may require dose adjustment based on blood sirolimus concentration, with the goal of keeping it between 5-15 ng/mL.	Inhibitor of mTOR. Inhibit insulin release and -cell growth via many methods that are still unknown.	Immunological suppression, mucositis, hyperlipidemia, increase of liver enzymes, thrombocytosis, and decreased immunological response to BCG vaccine were all seen.

Octreotide LAR/ Lanreotide	deep s.c	The dose is estimated using the cumulative current multi-injection dose of octreotide and administered as a single dose every four weeks, for a total dose of 15-60 mg/four weeks.	These long-acting somatostatin analogues work in the same way as daily multidose octreotide.	Similar to octreotide injections given on a daily basis. However, long-term outcomes are unknown.

Abbreviations: SUR1 is for sulphonlyurea receptor 1, KATP stands for adenosine triphosphate-sensitive potassium channels, s.c. stands for subcutaneous, i.m. stands for intramuscular, and i.v. stands for intravenous. SSTR2 stands for somatostatin receptors 2, and SSTR5 stands for somatostatin receptors 5. TSH stands for thyroid-stimulating hormone. BCG stands for Bacillus Calmette-Guérin, mTOR stands for mammalian target of rapamycin, and LAR stands for long-acting release

New Approaches in Hyperinsulinemic Hypoglycemia

Glucagon-like peptide 1 (GLP-1) is an incretin hormone that stimulates insulin secretion during satiety. In studies with Exendin (9-39), which is a GLP-1 receptor antagonist, significant increases in fasting glucose levels were obtained [43].

Today, various drug studies are still ongoing for HH. The results of studies such as monoclonal insulin receptor antibody (RZ358), SST5 receptor agonist (CRN0477), GLP1 receptor antagonist (exendin 9-39), Glucagon analogue (dasiglucagon), Long-acting glucagon analogue (HM15136) seem to open up horizons in the management of HH.

In conclusion, HH is the most common cause of permanent hypoglycemia in newborns. Rapid correction of hypoglycemia and maintenance of normoglycemia are vital because of potential brain damage and the risk of neuromotor developmental delay and epilepsy in the long term. It is vital to follow the developments in HH, which is an important entity in pediatric practice, and to take appropriate initiatives without wasting time.

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