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Congenital Hyperinsulinism in Infancy and Childhood: Pathophysiology, Diagnosis, and Management

So Hee Lee, Eun Ah Kim, Jin Kyung Kim

Department of Pediatrics, Daegu Catholic University School of Medicine, Daegu Catholic University Medical Center, Daegu, Korea

Congenital hyperinsulinism (CHI) is the leading cause of severe and persistent hypoglycemia in infants and children. Hyperinsulinemic hypoglycemia (HH) represents a clinically and genetically heterogeneous disorder, manifesting as transient forms related to perinatal stress or persistent forms caused by molecular defects in the genes regulating insulin secretion from pancreatic β-cell. Pathogenic variants in the K_{ATP} channel genes (*ABCC8, KCNJ11*) are the most frequent causes, although variants in other channels/transporter, metabolic enzymes, and transcription factors have also been reported. Syndromic forms associated multisystemic disorders also recognized. Prompt recognition of hypoglycemia, determination of its underlying etiology, and appropriate management are crucial to prevent irreversible neurodevelopmental impairment.

Key words: Hypoglycemia, Hyperinsulinism, Insulin, Diazoxide

REVIEW ARTICLE

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Correspondence to: Jin Kyung Kim, MD, PhD
Department of Pediatrics Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17 gil, Nam-gu, Daegu 42472, Korea
Tel: +82-53-650-4597
Fax: +82-53-650-4243
E-mail: kimjk@cu.ac.kr

ORCID
https://orcid.org/0000-0003-0018-851X

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INTRODUCTION

Hyperinsulinemic hypoglycemia (HH) is the most common cause of persistent hypoglycemia in infants and children. Dysregulated insulin secretion results in recurrent hypoglycemic episodes and suppression of ketone body production, which are an essential alternative fuels for the brain. Because the neonatal and infant brain has particularly high glucose requirements, these metabolic disturbances pose a substantial risk of hypoglycemia induced-brain injury. Timely recognition and appropriate management of hypoglycemia are therefore critical to prevent adverse neurodevelopmental outcomes. Congenital hyperinsulinism (CHI) represents a clinically and genetically heterogeneous condition that may present as either transient or persistent. Identifying the underlying etiology of HH is essential, as it guides therapeutic decision-making and defines the need for long-term follow-up [1-3].

Insulin release from Pancreatic β-Cells

Glucose enters pancreatic β-cells and is phosphorylated by glucokinase (GCK), which functions both as a metabolic enzyme and a glucose sensor. The resulting glucose-6-phosphate undergoes glycolysis to generate pyruvate, which enters the tricarboxylic acid (TCA) cycle and promotes ATP synthesis. The resulting increase in the intracellular ATP/ADP ratio leads to closure of ATP-sensitive potassium (K_{ATP}) channels, composed of Kir6.2 and SUR1 subunits, causing membrane depolarization, opening of voltage-dependent calcium channels (VDCCs), Ca^{2+} influx, and exocytosis of insulin granules [4,5]. The ability of glucose metabolism to elevate cytosolic Ca^{2+}, and thereby insulin secretion is referred to as the 'triggering pathway' (K_{ATP}-dependent pathway). Following calcium influx, insulin release

is further augmented by several 'amplification pathways', which include mitochondria-derived signals and receptors-mediated mechanisms [6,7].

Classification of Hyperinsulinism

Hyperinsulinism (HI) presenting in the immediate neonatal period may result from either genetic or acquired causes. Despite variation in clinical features, severity of hypoglycemia, and treatment durations, all forms of HI carry a significant risk of hypoglycemia-induced brain injury. HI is broadly categorized as transient or persistent. Persistent CHI is most often genetic, whereas transient forms are typically acquired and asso-

Table 1. Principle genes involed in congenital hyperinsulinism

Genes	Inheritance	Diazoxide-responsive	Features
K_{ATP} channnel protein			
ABCC8	AR, biallelic	No	Diffuse histology
KCNJ11			LGA,
			high GIR requirement
			protein-induced hypoglycemia,
	AR, monoallelic*	No	Focal histology
			approximately 50% LGA,
			moderate-high GIR requirement
			protein-induced hypoglycemia
	AD	No	Diffuse histology
			Clinically indistinguishable recessive form
	AD	Yes	Diffuse histology
			Milder phenotype with less severe hypoglycemia, lower GIR requirement, protein-induced hypoglycemia
Ion & solute transporters			
KCNQ1	AD/AR	Yes	Diffuse histology, Hereditary long QT syndrome, deafness, gastrointestinal defects
CACANA1D	AD	Yes	Diffuse histology, Heart defect, Severe hypotonia
SLC16A1	AD	Yes	Diffuse histology, exercise induced HI
Enzyme and regulators of vesicle release			
GLUD1	AD	Yes	Diffuse histology
			Hyperinsulinemia hyperammonemia syndrome
			Protein induced hypoglycemia
GCK	AD	Variable	Diffuse /Atypical histology
			Ketotic hypoglycemia with prolonged fasting
			Variable severity and age of onset
HADH	AR	Yes	Diffuse histology
			Elevated plasma 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutaric acid.
			Protein-induced hypoglycemia
HK1	AD	Yes	Diffuse histology, isolated HI
PMM2	AR	Yes	Diffuse histology, Polycystic kidney
PGM1	AR		Diffuse histology, Postprandial and fasting hyperketotic hypoglycemmia
Transcription factor			
HNF1A	AD	Yes	Diffuse histology, Risk for Diabetes (MODY 1)
HNF4A	AD	Yes	Diffuse histology, Risk for Diabetes (MODY 3)
FOXA2	AD	Yes	Diffuse histology, Hypopituitarism
EIF2S3	X-linked	Yes	Diffuse histology, Hypopituitarism

AR, autosomal recessive; AD, autosomal dominant; K_{ATP}, adenosine triphosphate-sensitive potassium channel; LGA, large for gestational age; GIR, glucose infusion rate; *ABCC8*, ATP-Binding Cassette Subfamily C Member 8; *KCNJ11*, Potassium Inwardly-Rectifying Channel Subfamily J Member 11; *KCNQ1*, Potassium voltage-gated channel subfamily Q member 1; *CACANA1D*, Calcium voltage-gated channel subunit alpha1 D; *SLC16A1*, solute carrier family16 member 1; *GLUD1*, Glutamate Dehydrogenase 1; *GCK*, glucokinase; *HADH*, hydroxyacyl-coenzyme A dehydrogenase; *HK1*, hexokinase1; *PMM2*, Phosphomannomutase 2; *PGM1*, Phosphpglucomutase 1; *HNF4A*, hepatocyte nuclear factor 4 alpha; *HNF1A*, hepatocyte nuclear factor 1 alpha; *FOXA2*, Forkhead box A2; *EIF2S3*, Eukaryotic translation initiation factor 2 subunit gamma.
*Paternally inherited recessive mutation with somatic loss of maternal 11p15 region, resulting in paternal isodisomy, and localized β-cell proliferation.

ciated with perinatal risk factors such as maternal diabetes, birth asphyxia, intrauterine growth restriction, prematurity, erythroblastosis fetalis, maternal medications (e.g., sulfonylureas, beta-blockers), or intrapartum glucose infusion [2]. Perinatal stress–induced HI represents an exaggerated form of transitional hypoglycemia caused by hypoxia-mediated lowering of the β-cell glucose threshold for suppression of insulin secretion. Transient HI generally resolves within days to weeks but may persist for several months, and severe cases occasionally require diazoxide therapy [8,9].

Clinically, HI can also be classified according to the response to diazoxide, the first line pharmacological agent for managing hypoglycemia. Up to 90% of diazoxide-unresponsive cases harbor *ABCC8* or *KCNJ11* mutations [10], making unresponsiveness a strong indicator of an underlying genetic etiology. Based on histological features, CHI can be categorized into diffuse, focal, and atypical variants, depending on the extent and distribution of β-cell hyperplasia within the pancreas. The focal form is characterized by localized islet cell hyperplasia, the diffuse form involves the entire pancreas, and atypical CHI lacks clear features of either type [2].

Genetic etiology

Genetic forms of HI typically present in the neonatal period, although some cases may remain undiagnosed until later infancy or childhood. The estimated incidence of non-syndromic genetic HI is approximately 1 in 25,000–45,000 newborns [3]. Pathogenic variants have been identified in genes encoding pancreatic β-cell ATP-sensitive potassium (K_{ATP}) channels, other channels and transporters, enzymes, and transcription factors [2] (Table 1).

ABCC8 (ATP-Binding Cassette Subfamily C Member 8) or *KCNJ11* (Potassium Inwardly-Rectifying Channel Subfamily J Member 11)

The most common and severe form of monogenic HI results from dysfunction of the adenosine triphosphate-sensitive potassium channel (K_{ATP}) caused by inactivating mutations of the *ABCC8* or *KCNJ11* genes, which encode the SUR1 and Kir6.2 subunits of the K_{ATP} channel, respectively [11,12]. These variants may be inherited in recessive or dominant patterns.

Infants with K_{ATP}-channel mutations are typically large for gestational age, often requiring high glucose infusion rates to maintain euglycemia. Biallelic recessive mutations abolish K_{ATP} channel expression, leading to diffuse, diazoxide-unresponsive HI [13]. Monoallelic paternal recessive mutations, with combined somatic loss of the maternal 11p15 region, result in focal HI through a 'two-hit' mechanism that produces paternal uniparental disomy and localized β-cell proliferation [14,15]. Monoallelic dominant mutations permit normal channel trafficking but impair function. Variants that markedly diminish channel activity cause diazoxide-unresponsive HI, whereas those retaining partial activity may result in diazoxide-responsive. Clinically, biallelic recessive and dominant diazoxide-unresponsive K_{ATP}-HI are indistinguishable at presentation [13]. Although diffuse K_{ATP}-HI is generally diazoxide unresponsive, rare patients with compound heterozygous *ABCC8* mutations have shown diazoxide responsiveness or spontaneous remission [16-18]. Conversely, activating mutations in *ABCC8* or *KCNJ11* have the opposite effect, impairing insulin secretion and leading to neonatal diabetes or maturity-onset diabetes of the young (MODY) [19].

SLC16A1 (solute carrier family16 member 1)

The *SLC16A1* gene encodes monocarboxylate transporter 1 (MCT1), which facilitate the cellular uptake of monocarboxylate such as pyruvate and lactate. Under normal physiological conditions, *SLC16A1* expression is silenced in pancreatic β-cells to prevent inappropriate insulin secretion during anaerobic exercise. Activating promoter mutations in *SLC16A1* leads to aberrant β-cell expression of MCT1, allowing pyruvate to enter the TCA cycle, increase ATP production, and stimulate insulin release. This results in exercise induced hyperinsulinism (EIHI), characterized by hypoglycemic episodes, occurring within 3-5 min after strenuous physical activity [20].

GLUD1 (Glutamate Dehydrogenase 1)

The second most common genetic cause of CHI is activating mutations in GLUD1, which encodes glutamate dehydrogenase (GDH). These mutations impair guanosine-5′-triphosphate (GTP)-mediated inhibition of GDH, leading to increased conversion of glutamate to α-ketoglutarate and ammonia. The enhanced entry of α-ketoglutarate into the TCA cycle increases ATP production, thereby stimulating inappropriate insulin secretion. GDH activity is physiologically inhibited by GTP and short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD), and allosterically activated by leucine, explaining the protein- and fasting induced hypoglycemia seen in these patients [2,6,13]. Most cases are mild and diazoxide responsive. Affected individuals typically present late infancy with hyperinsulinism–hyperammonemia (HI/HA) syndrome [21], characterized by postprandial hypoglycemia after protein-rich meals, fasting hy-

poglycemia, with moderate elevated plasma ammonia, increased urinary α-ketoglutarate. Seizures, learning disabilities, and attention deficit hyperactivity disorder are also observed [2,6,13,21].

GCK (Glucokinase)

GCK catalyzes the phosphorylations of glucose to glucose-6-phosphate, thereby entering glycolysis and promoting ATP production, which subsequently triggers insulin secretion. Activating mutations in *GCK* lower the glucose threshold for insulin release, causing hyperinsulinemic hypoglycemia of variable severity [22]. The response to diazoxide is variable. Affected individuals may develop ketotic hypoglycemia during prolonged fasting, in contrast to the hypoketotic hypoglycemia characteristic of other forms of HI [23]. Conversely, inactivating mutations in *GCK* reduce β-cell glucose sensitivity and cause neonatal diabetes or maturity-onset diabetes of the young (MODY) [19].

HADH (Hydroxyacyl-CoA Dehydrogenase)

HADH encodes SCHAD, an enzyme that normally exerts an inhibitory effect on GDH. Biallelic loss of function mutation in *HADH* impair this inhibition, resulting in increased GDH activity, enhanced ATP production, and inappropriate insulin secretion. The clinical phenotype resembles GDH-HI, presenting with fasting- and protein-induced hypoglycemia but without hyperammonemia. Disease severity is variable, ranging from severe neonatal CHI to later-onset, protein-sensitive, diazoxide-responsive forms. Characteristic biochemical features may include elevated plasma 3-hydroxybutyrylcarnitine and urinary 3-hydroxyglutaric acid [24].

HK1 (hexokinase1)

HK1 encodes a glycolytic enzyme that catalyse the phosphorylation of glucose to glucose 6 phosphate. It is broadly expressed across most tissues but is normally silenced in the liver and pancreatic β-cell. Activating mutations in non-coding regulatory regions of *HK1* cause loss of gene repression, leading to inappropriate β-cell expression of hexokinase and dysregulated insulin secretion, resulting in HI [25]. Most affected individuals respond to diazoxide [3].

HNF4A (hepatic nuclear factor 4 alpha) and *HNF1A* (hepatic nuclear factor 1 alpha)

Dominant Inactivating mutations in *HNF4A* and *HNF1A* cause diazoxide-responsive form HI, often presenting with neonatal hypoglycemia that resolves during early childhood [26]. These transcription factor variants are also well-recognized causes of MODY (MODY1 and MODY3), and affected individuals remain at risk of diabetes later in life, even when neonatal HI is transient. In families with a history suggestive of MODY, genetic testing for *HNF1A* and *HNF4A* is recommended [3].

Syndromic forms

In a small portion of CHI cases, HI occurs occurs as part of syndromic or multisystemic diseases. including overgrowth syndromes (e.g. Beckwith-Wiedemann and Sotos syndromes), chromosomal and monogenic developmental syndromes with postnatal growth failure (e.g. Turner syndromes, Kabuki syndromes, and Costello syndromes), congenital disorders of glycosylation, and syndromic channelopathies (e.g. Timothy syndrome). The underlying HI mechanisms in these conditions remain unclear, and the metabolic abnormalities are transient [27].

DIAGNOSIS

Diagnosis of CHI is based on clinical presentation and characteristic biochemical findings obtained during hypoglycemia. Evidence of excessive insulin action at the time of hypoglycemia (plasma glucose <50 mg/dL) include suppressed plasma β-hydroxybutyrate (<1.8 mmol/L), free fatty acids (<1.7 mmol/L), an inappropriately large glycemic response to glucagon (≥ 30 mg/dL), an increased glucose infusion requirement to maintain normoglycaemia (>8 mg/ kg/min in neonate, >3 mg/kg/min in adults). Evidence of excessive or inadequate suppressed insulin secretion include detectable plasma insulin (≥ 1.25 μU/mL), and C-peptide (≥ 0.5 ng/mL), although these are less definitive than the evidence of excessive insulin action. Insulin concentration do not always correlate with biochemical evidence of insulin action; therefore, interpretation should be based primarily on the metabolic indicators of insulin action,rather than absolute insulin levels. A low or undetectable insulin level durin hypoglycemia does not exclude HI [2,3].

In neonates, evaluated before 72 hours of life, repeat testing after this period is recommended if hypoglycemia persists, to exclude transient neonatal hypoglycemia [2,3]. Infants with CHI are often large for gestational age and require high glucose infusion rates (>10 mg/kg/min), however, some may have normal birth weight, milder glucose requirements, and

present with hypoglycemia later in infancy [2,3].

Diffuse forms of CHI typically present with higher birth weights and greater glucose requirements, whereas, approximate half of those with focal form are large for gestational age [28]. Because of substantial clinical overlap, focal and diffuse forms cannot be reliably distinguished by clinical features alone.

Genetic testing is recommended when acquired causes are unlikely, particularly in diazoxide-unresponsive cases or in diazoxide-responsive cases persisting beyond three months. Identification of *ABCC8* and *KCNJ11* mutations is important for with diazoxide-unresponsive HI, as a paternally inherited mutations predicts focal forms with approximately 97% sensitivity [10]. Pancreatic imaging with ^{18}F-DOPA PET Scanning is useful for localizing potentially resectable focal lesions, although very small lesions may remain undetected, and a negative scan does not exclude focal disease [29].

TREATMENT

Despite efforts to maintain plasma glucose within taget range of 70–100 mg/dL, studies have shown that levels may fall below this threshold in up to 15%–20% of measurements in children with severe HI. In such cases, a lower glycemic target of approximately 63 mg/dL may be acceptable, depending on the frequency and severity of hypoglycemia and the availability of alternative therapeutic strategies [3]. Diazoxide remains the first-line pharmacological agent for the management of HH. However, patients with homozygous or compound heterozygous recessive mutations of *ABCC8* or *KCNJ11* causing diffuse CHI are typically unresponsive to diazoxide [10]. Octreotide, a somatostatin analogue, is used as a second-line agent, whereas lanreotide, glucagon, acarbose, sirolimus or everolimus may be considered in refractory cases. Surgical intervention is indicated when medical therapy fails [2,3]. Focal K_{ATP}-HI can be cured by limited resection, whereas diffuse CHI requires continued medical management, with near-total pancreatectomy reserved for severe, medically intractable cases. In large surgical cohorts, focal and diffuse types accounted for approximately 55% and 45% of cases, respectively [30]. Following near-total pancreatectomy, hypoglycemia recurs in up to 50%-60% of patients. Most achieve adequate glycemic control with adjunctive medical therapy, although a subset may require repeat surgery, Over time, nearly all patients eventually develop insulin-dependent diabetes [2,3].

CONCLUSION

Effective therapeutic options for CHI remain limited, and affected children continue to experience a high incidence of neurological sequelae due to hypoglycemia-induced brain injury. Improving long-term outcomes requires prompt recognition of hypoglycemia, accurate identification of underlying cause, timely initiation of appropriate treatment. Genetic diagnosis is essential for defining etiology, predicting phenotype, guiding targeted management.

AUTHOR CONTRIBUTIONS

Conceptualization and Investigation: Lee SH, Kim EA. Writing-original draft preparation: Lee SH, Kim EA. Writing-review and editing: Kim JK. All authors have read and agreed to the published version of the manuscript.

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