(別表 1)観察・検査スケジュール

		登録時	治療前 2 週以内	治療開始時	1 週後 (±2 日)	2 週目から 4 週後	5 週目から研究期間終了時*1 までの治療継続中	治療終了時	治療終了後 1 年以内*4
頻度		1 回	1 回	1 回	1 回	1 回/1 週(±3 日)	1 回/3 か月 (±3 週)	1 回(±3 週)	期間中 1 回
患者背景・診断時臨床所見		○							
併用薬・併用治療*2 の内容				○	○	○	○	○	
有害事象					○	○	○	○	
オクトレオチド投与法 (持続 or 頻回)				○	○	○	○	○	
オクトレオチド投与量 (μg/kg/日)				○	○	○	○	○	
平均ブドウ糖静注量 (g/kg/日)				○	○	○	○	○	
臨床検査									
検査頻度			1 回	1 回	1 回	1 回/1 週 (±3 日)	1 回/3 か月 (±3 週)	1 回	期間中 1 回
身体計測	体重		○	○	○	○	○	○	○
	身長					○ (期間中 1 回)	○		○
	頭囲								○
血糖値*3			○		○	○	○	○	
末梢血液像 (血算、白血球分画)			○			○	○	○	
血液生化学 (Na、K、Cl、Ca、AST、ALT、ALP、TBil、DBil、BUN、CRE、TP、ALB)			○			○	○	○	
その他検査									
腹部超音波検査							○ (期間中 1 回)		
発達評価								○ (治療開始後 1 年以上経過後 1 回) *1	

＊1 平成 29 年 3 月 31 日まで
＊2 他の低血糖に対する治療については、経腸栄養、グルカゴン皮下注射・静脈注射、グルココルチコイド投与、カルシウム拮抗剤、膵切除のいずれかとする。
＊3 血糖値はいずれも哺乳前 (又は食前)、ただし持続ブドウ糖輸液・持続注入は続行可とする。簡易血糖測定値・血清血糖測定値・血漿血糖測定値の区別を記載する。
＊4 観察期間終了後 1 年以内のデータが複数ある場合は、最も遅い時期の数値を当該ポイントのデータとする。

先天性高インスリン血症に対する
オクトレオチド皮下注射療法レジストリ
(SCORCH レジストリ)

実施計画書　別冊
(研究の実施体制)

研究代表者：依藤　亨
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2015 年 4 月 1 日(Ver.3.0)

1. 研究の主体

大阪市立総合医療センター小児代謝・内分泌内科および臨床研究センターが実施の主体となる。

2. 研究事務局／データセンター

大阪市立総合医療センター 臨床研究センターにおく。

研究代表者

大阪市立総合医療センター小児代謝・内分泌内科　部長	依藤　亨

担当者

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FAX：06-6929-1090 平日 9～17 時（祝祭日、土曜・日曜、年末年始は受け付けない）
URL：http://byouin-city-osaka.jp

3. 研究参加施設／研究責任医師

研究責任医師は、本臨床研究の実施に係る医師を指名することとする。

分担研究機関

大阪市立総合医療センター　小児代謝・内分泌内科　部長	依藤　亨
国立成育医療研究センター　生体防御系内科部　部長	横谷　進
浜松医科大学　小児科　教授	緒方　勤
獨協医科大学　小児科　教授	有坂　治
東京都立小児総合医療センター　内分泌代謝科　部長	長谷川　行洋
木沢記念病院　小児科　部長	増江 道哉

4. 遺伝子検査実施機関

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TEL：06-6929-1221

5. 18F-DOPA PET 実施機関

木沢記念病院
岐阜県美濃加茂市古井町下古井 590
TEL：0574-25-2181

6. 統計専門家

獨協医科大学　医学部　公衆衛生学講座　准教授　西連地 利己
国立成育医療研究センター　臨床研究開発センター　データ管理部
生物統計室　室長　井上　永介

7. 研究進行に関する評価

研究事務局は、研究の進行について下記よりなるアドバイザリーコミッティーに 6 か月に 1 度報告し、その評価、進言を受ける。

緒方　勤（日本小児内分泌学会理事長、浜松医科大学）
大薗　恵一（日本小児内分泌学会副理事長、大阪大学）
横谷　進（日本小児内分泌学会前理事長、国立成育医療研究センター）
有阪　治（日本小児内分泌学会理事、薬事委員会委員長、獨協医科大学）
長谷川行洋（日本小児内分泌学会理事、あり方委員会委員長、東京都立小児総合医療センター）

楠田　聡（東京女子医科大学母子総合医療センター　所長・教授）

第3回班会議　議事録

日時：2014年11月28日　12時20分～13時30分

場所：大宮ソニックシティ7階 707号室

出席者：長谷川行洋（都立小児総合医療センター）、細川悠紀（大阪市立総合医療センター）、依藤亨（大阪市立総合医療センター）横谷進（国立成育研究医療センター）

（五十音順、敬称略）

1．F-DOPA PETのまとめ…依藤先生より（木沢記念病院　増江先生の文献、スライド）

- CHI31例のPETの結果を日児誌にまとめた概要を説明。

2．研究の進捗状況

- 2013年8月レジストリ開始後、登録施設12施設、登録症例14例となっている。
  有害事象延べ21件で嘔吐、白色便、高血糖など予想されたもので、重篤な有害事象なし。
- 2014年1月スタディ開始、先進医療承認に時間を要し、現時点で協力医療機関としての登録数は18施設、承認予定が2施設。
  症例は6月に1例目登録後、現在4例が登録されている。

3．スタディの登録症例について

S-01, S-02は大阪市立総合医療センターで実施。初期治療に反応せず無効例として中止。
S-03,S-04は現在初期治療中で効果は現時点では未報告である。
無効例の問題点としては先行研究で最も多かった父由来片アリル変異の局所型でなかったことが上げられる。（S-01は変異なし、S-02は母由来dominant type）
先行研究とこれらの2例の差を考えると、症例数を増やして検討する必要があるかもしれない。（但し症例数を増やすためには試験期間の延長と研究資金が必要）

4．協議事項

- レジストリについて
  症例数は14/15例で不十分であり、継続が必要。
  レジストリの延長はPMDAへの連絡とUMINの登録変更をする必要がある。
  ＞保険承認の目的のほかにも学術的な意味で本疾患の長期予後を調査する必要があり、その体制を学会主導でサポートしてはどうか。（長谷川）

- スタディについて
  症例数4/5例と不十分である上に、最後の症例が入って最低1年のフォローが必要なので、試験期間延長は必須。

近々先進医療延長届を行うが、費用面の記載は厚労科研費を申請予定と書くことになる。(科研費の結果がわかるのは3月頃)
プロトコル変更は行わず、期間の延長のみ行う予定。(最低1年延長)
費用の面のめどが立つようであれば、症例数も増やす。

- 2014年1月のサイトビジットでの指摘事項
  - ノバルティスに承認申請の確約を取る＞社会的な問題から現在ノバルティスとの接触は避けた方がいいと多方面からアドバイスされているため、この件は保留。
  - 生物統計家をいれる＞成育医療研究センターに採用予定の統計家に依頼する。
  - SDVが必要ではないか？＞費用面の問題があり、厚労科研など延長試験の原資が決まった時点で検討する。

[IV] 研究成果の刊行に関する一覧表

学 会 等 発 表 実 績

委託業務題目「先天性高インスリン血症に対するオクトレオチド持続皮下注療法の有効性・安全性に関す

機関名 大阪市立総合医療センターほか

１．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
小児の低血糖症：update（口演）	依藤　亨	第24回臨床内分泌代謝Update（大宮）	2014年11月	国内
小児低血糖の診かた（口演）	依藤　亨	第28回近畿小児科学会（大阪）	2015年2月	国内

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
Congenital hyperinsulinism: current status and future perspectives.	Yorifuji T.	Annals Pediatr Endocrinol Metab 2014, 19; 57-68.	2014年6月	国外
Congenital hyperinsulinism: Global and Japanese perspectives.	Yorifuji T Masue M Nishibori H.	Pediatr Int. 2014; 56(4):467-76.	2014年8月	国内・国外
先天性高インスリン血症の18F-DOPA PETによる局在診断と治療予後	増江道哉 西堀弘記 高田勲矢 依藤　亨	日本小児科学会雑誌 2014, 118; 1342-1349.	2014年9月	国内

[V] 班員名簿

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	増江道哉	木沢記念病院小児科　部長
	西堀弘記	木沢記念病院放射線科　部長

[VI] 主要原著論文別冊

Review article

http://dx.doi.org/10.6065/apem.2014.19.2.57
Ann Pediatr Endocrinol Metab 2014;19:57-68

Annals of Pediatric Endocrinology & Metabolism
apem

Congenital hyperinsulinism: current status and future perspectives

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The diagnosis and treatment of congenital hyperinsulinism (CHI) have made a remarkable progress over the past 20 years and, currently, it is relatively rare to see patients who are left with severe psychomotor delay. The improvement was made possible by the recent developments in the understanding of the molecular and pathological basis of CHI. Known etiologies include inactivating mutations of the K_{ATP} channel genes (*ABCC8* and *KCNJ11*) and *HNF4A*, *HNF1A*, *HADH*, and *UCP2* or activating mutations of *GLUD1*, *GCK*, and *SLC16A1*. The understanding of the focal form of K_{ATP} channel CHI and its detection by ^{18}F-fluoro-L-DOPA positron emission tomography have revolutionized the management of CHI, and many patients can be cured without postoperative diabetes mellitus. The incidence of the focal form appears to be higher in Asian countries; therefore, the establishment of treatment systems is even more important in this population. In addition to diazoxide or long-term subcutaneous infusion of octreotide or glucagon, long-acting octreotide or lanreotide have also been used successfully until spontaneous remission. Because of these medications, near-total pancreatectomy is less often performed even for the diazoxide-unresponsive diffuse form of CHI. Other promising medications include pasireotide, small-molecule correctors such as sulfonylurea or carbamazepine, GLP1 receptor antagonists, or mammalian target of rapamycin inhibitors. Unsolved questions in this field include the identification of the remaining genes responsible for CHI, the mechanisms leading to transient CHI, and the mechanisms responsible for the spontaneous remission of CHI. This article reviews recent developments and hypothesis regarding these questions.

Keywords: Hyperinsulinism, Congenital, Hypoglycemia

Introduction

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy, and severe hypoglycemia in infancy can cause permanent brain damage[1-4]; therefore, optimal management is extremely important. In the past, our armamentarium against severe CHI was very limited. With only diazoxide and near-total pancreatectomy as available options, many patients were left with psychomotor delay or epilepsy. Even worse, a number of patients developed postoperative insulin-dependent diabetes mellitus[3,5,6].

Over the past 20 years, however, remarkable progress has been made in the diagnosis and management of CHI, which has directly translated into improved neurological outcomes for patients[3,7]. This improvement in the understanding of the pathogenesis of CHI and the development of diagnostic modalities have helped in deciding the optimal management strategy for each patient[8-10]. However, the situation is still far from ideal. Several unsolved questions and unmet needs remain.

In this review, I first discuss the diagnostic criteria and the practical treatment goals for CHI, which are the prerequisites for all subsequent management. Then, after a brief introduction of

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the mechanism of glucose-induced insulin secretion, I review the current status of the understanding and management of CHI. Finally, I list some of the unsolved questions in this field and introduce key findings that may guide us in the future.

Diagnostic criteria and treatment goals for CHI

1. Diagnosis of CHI (Table 1)

To diagnose hyperinsulinemic hypoglycemia (HI), physicians rely both on clinical clues to identify hyperinsulinism and on laboratory tests to prove hyperinsulinemia.

1) Clinical clues to suspect HI

The presence of HI may be suspected even when the patient is still in an emergency room by asking three questions: When did hypoglycemia develop after the last meal? Does the patient respond to glucagon injection? What is the amount of glucose infusion needed to keep the patient euglycemic?

(1) When did hypoglycemia develop after the last meal?

Euglycemia is maintained by a balance between hepatic glucose output and peripheral uptake induced by insulin. Hepatic glucose output is determined by three factors: food absorption, glycogenolysis, and gluconeogenesis. Fig. 1 shows the duration of glucose production by each of these mechanisms. In disorders of glycogenolysis, the patient typically becomes hypoglycemic after 4–5 hours of fasting. Similarly, in disorders of gluconeogenesis, the patient typically develops hypoglycemia after an overnight fast. When the patient has hyperinsulinemia, hypoglycemic episodes can occur at any time point, sometimes even at 2 hours after the last meal.

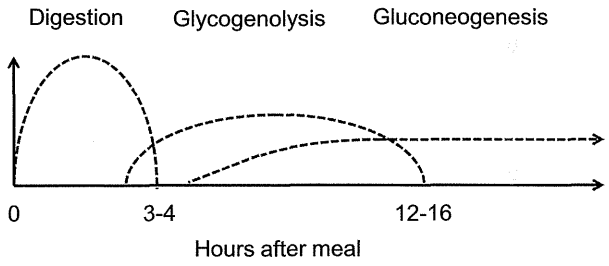

Fig. 1. Glucose source during fasting.

(2) Does the patient respond to glucagon injection?

When hypoglycemia is caused by a defect in glycogenolysis, the patient does not respond to intramuscular/intravenous injection of glucagon, which stimulates glycogenolysis. Similarly, when a patient has a defect in gluconeogenesis, by the time the patient becomes hypoglycemic, the glycogen storage in the liver should have been exhausted; therefore the patient does not respond to glucagon either. Only when the patient has hyperinsulinemia can hepatic glycogen be mobilized by glucagon, and glycemic response (>1.7–2.0 mmol/L) is seen.

(3) What is the amount of glucose infusion needed to keep the patient euglycemic?

When hypoglycemia is caused by etiologies other than hyperinsulinism, euglycemia should be maintained by providing the amount of intravenous glucose that corresponds to the normal hepatic (or possibly renal) glucose output: 4–6 mg/kg/min in neonates, 1–2 mg/kg/min in adults, and intermediate values in older children. When euglycemia cannot be maintained by these amounts of continuous glucose infusion, clinicians may suspect the presence of hyperinsulinemia.

2) Laboratory evidence of hyperinsulinism

(1) Insulin at hypoglycemia

HI is diagnosed by demonstrating inappropriately elevated insulin in the presence of hypoglycemia (<2.5 mmol/L, 45 mg/dL). However, it is often difficult to prove hyperinsulinemia by a critical sample taken during a hypoglycemic event[11,12]. In addition, the term "inappropriately elevated" insulin level is not precisely defined: some authors suggest that any detectable level of insulin is abnormal[8,9], whereas others propose different cutoffs[13]. With regard to the insulin levels during hypoglycemia, "any detectable level" is probably an overstatement because it may suggest but not prove HI. The cutoffs depend on the sensitivity of the particular assay as well as on the insulin sensitivity of each patient. In our own series of 94 confirmed Asian patients with CHI, the insulin at hypoglycemia ranged

Table 1. Diagnosis of hyperinsulinemic hypoglycemia

	Serum insulin at hypoglycemia, pmol/L (μU/mL)	Glucose infusion rate to maintain euglycemia (mg/kg/min)	Glycemic response to glucagon, mmol/L (mg/dL)	Free fatty acid/ketone bodies	Ref.
1	ND	>8	>1.5 (27)	ND	10
2	Any detectable level	>10 (neonate) >7 (5 years old), >4 (adults)	>1.7 (30)	Inappropriately low fatty acids and ketones	9
3	>6.95 (1)	ND	>2–3 (36–54)	Negative ketone bodies in urine/plasma	13
4	Any detectable level	>8	ND	ND	8
Proposed criteria	>20.84 (3)	>8 (neonates), >3 (adults), in-betweens (children)	>2 (36)	3-hydroxybutylate < 1.3 mmol/L, FFA < 1 mmol/L	

ND, not described; FFA, free fatty acid.

8.75–1,250 pmol/L (1.26–180 μU/mL) with a median of 73.3 pmol/L (10.55 μU/mL; unpublished data). In contrast, insulin levels during hypoglycemic events in patients without HI ranged from undetectable to 43.1 pmol/L (6.2 μU/mL) while the detection limit was >2.1 pmol/L (0.3 μU/mL). Clearly, these values overlap.

(2) Relatively low free fatty acid and ketone bodies at hypoglycemia

Insulin inhibits lipolysis; therefore, low free fatty acid and ketone bodies during hypoglycemia are also used as diagnostic adjuncts. In normal infants (0–24 months of age), blood 3-hydroxybutylate and free fatty acid levels after a 20-hour fast are 3.11 mmol/L (range, 1.29–4.34 mmol/L) and 2.15 mmol/L (range, 1.03–3.24 mmol/L), respectively[14]. These values can be used to set cutoffs for HI. In our series of 207 cases with confirmed CHI, the highest 3-hydroxybutylate at hypoglycemia was 0.44 mmol/L (unpublished data).

3) Proposed diagnostic criteria to suspect HI

It is difficult to set definitive diagnostic criteria for HI. Several authors propose different cutoff values to diagnose HI (Table 1), but these criteria should be regarded as suggestive and not necessarily diagnostic. The bottom of Table 1 includes proposed criteria that strongly suggest the presence of HI in children.

2. Treatment goals of CHI

The goals of HI treatment are to prevent neurological sequelae of hypoglycemia. Factors that could affect neurological outcomes include age, comorbid conditions, severity of the initial episode, and duration and frequency of subsequent hypoglycemic episodes[15-18]. Therefore, the treatment goals should be individualized. Currently, blood glucose >3.33–3.89 mmol/L (60–70 mg/dL) is the most commonly recommended target for HI treatment[10,11,13].

Insulin secretion and the ATP-sensitive potassium channel

1. Glucose induced insulin secretion (the GSIS pathway) (Fig. 2)

In pancreatic β-cells, extracellular glucose is transported into the cytoplasm by the action of glucose transporter (GLUT2). The glucose is then phosphorylated by glucokinase. Glucokinase is not easily saturated by the physiological range of intracellular glucose, and is not inhibited by its end product glucose-6-phosphate. Therefore, it serves as the fuel gauge of the β-cells. Glucose-6-phosphate is then metabolized via glycolysis, the Krebs cycle, and oxidative phosphorylation to generate ATP. An increased ATP/ADP ratio within β-cells leads to the closure of the ATP-sensitive potassium channel (K_{ATP} channel), which causes depolarization of the cell membrane and opening of the voltage-gated calcium channel. The resulting influx of calcium ions then causes fusion of the insulin secretory granules with the cell membrane and secretion of insulin[19].

2. The K_{ATP} channel

The K_{ATP} channel is an octameric structure composed of four molecules of pore-forming Kir6.2 and four molecules of SUR1 that surround the pore and regulate the channel activity.

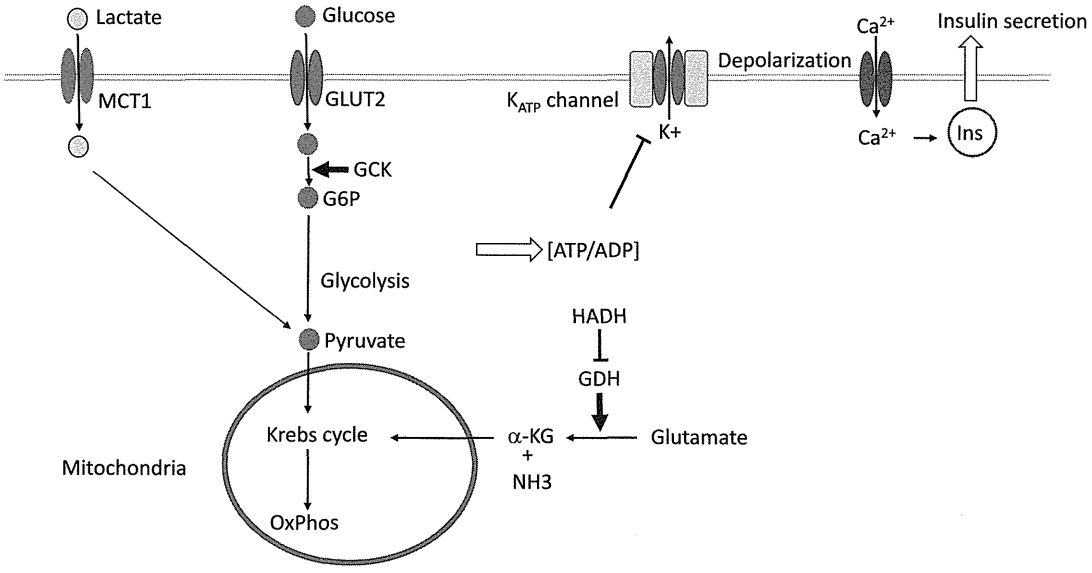

Fig. 2. The glucose-induced insulin secretion pathway. GLUT2, glucose transporter 2; GCK, glucokinase; G6P, glucose 6-phosphate; MCT1, monocarboxylate transporter 1; GDH, glutamate dehydrogenase; HADH, L-3-hydroxyacyl-coenzyme A dehydrogenase; α-KG, α-ketoglutarate; Ins, insulin.

Intracellular ATP binds to Kir6.2 molecules to inhibit the channel activity, whereas MgADP binds to SUR1 to activate the channel. Therefore, channel activity is controlled by the ATP/ADP ratio within the cells.

In the endoplasmic reticulum, Kir6.2 and SUR1 associate with each other to form the channel that is transferred to the Golgi apparatus and to the cell surface. If Kir6.2 and SUR1 do not associate with each other, they cannot escape the endoplasmic reticulum and are degraded there.

Kir6.2 and SUR1 are encoded by *KCNJ11* (1 exon) and *ABCC8* (39 exons), respectively. These genes are located side-by-side with close proximity on 11p15.1.

Known etiologies of CHI (Table 2)

1. Transient and persistent CHI

There are two main types of CHI: transient CHI, which usually develops soon after birth and resolves spontaneously within the first 3–4 weeks of life and persistent CHI, which can develop later in life as well as in the neonatel period, and lasts longer. The distinction between transient and persistent CHI is not possible on the basis of laboratory test results. In our national survey in Japan, only shorter gestational age and lighter birth weight were predictors of transient CHI[20]. The incidence of persistent CHI is generally estimated as 1 in 50,000 live births[9] although the incidence could be higher in certain populations (e.g., 1 in 2,500 births in Saudi Arabia). On the contrary, the incidence of transient CHI is much higher. In the national survey in Japan, the incidence of transient CHI (1 in 17,000 births) was approximately twice as high as that for persistent CHI (1 in 35,400 births)[20].

1) Transient CHI

Transient CHI is believed to be caused mainly by nongenetic factors, e.g., small size for the infant's gestational age or stressful perinatal conditions such as cardiopulmonary disorders. An important exception is the monoallelic inactivating mutation in *HNF4A*[21-23]. Unlike other patients with transient CHI, patients with *HNF4A* mutations are often born large for gestational age. Importantly, a fraction of these patients develop a form of dominantly inherited diabetes, maturity-onset diabetes of the young type 1 (MODY1), later in life and therefore should be followed up after resolution of CHI (21-23). Because *HNF1A* is in the same pathway with *HNF4A* and its mutation is the cause of MODY3, researchers checked for mutations in *HNF1A* in patients with transient CHI, and indeed found some patients with mutations in *HNF1A*[24,25].

2) Persistent CHI

In contrast, persistent CHI is believed to have genetic etiologies. However, even with the most comprehensive analysis, the responsible genes can be identified in only 53% of diazoxide-responsive CHI patients[26] although in unresponsive patients, K_{ATP} channel mutations could be identified in most (87.6%–88%) cases[26,27].

2. Causes of persistent CHI

Table 2 lists known causes of CHI. The most common of these are inactivating mutations in one of the K_{ATP} channel genes, *ABCC8* or *KCNJ11* (K_{ATP}-CHI). The second most common is an activating mutation of glutamate dehydrogenase (GDH-CHI). Others are relatively rare. When confined to families with consanguinity, inactivating mutations in L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH-CHI) are the most common cause[26,27].

1) K_{ATP}-CHI

Three distinct subtypes of K_{ATP}-CHI are known:

(1) Recessively-inherited K_{ATP}-CHI: Recessive K_{ATP}-CHI is caused by biallelic mutations in one of the K_{ATP} channel genes. This is the most severe form of K_{ATP}-CHI, and all β-cells in the pancreas present in abnormal (diffuse) form. Pathologically, recessive K_{ATP}-CHI is characterized by large β-cells with abnormally enlarged nuclei[28].

Table 2. Genetic causes of congenital hyperinsulinism

Gene	Protein	Chromosome	Inheritance	Note
K_{ATP} channel			AR, AD, Focal	Diazodixe unresponsive Usher CHI (contiguous deletion)
ABCC8	SUR1	11p15.1		
KCNJ11	Kir6.2	11p15.1		
GLUD1	Glutamate dehydrogenase	10q23.3	AD	Hyperammonemia
GCK	Glucokinase	7p15	AD	Diffuse/focal?
HADH	L-3-hydroxyacyl-coenzyme A dehydrogenase	4q22–q26	AR	
UCP2	Uncoupling protein 2	11q13	AD	
SLC16A1	Monocarboxylate transporter 1	1p12	AD	Exercise induced HI
HNF4A	Hepatocyte nuclear factor 4α	20q13.12	AD	Transient/persistent macrosomia
HNF1A	Hepatocyte nuclear factor 1α	12q24.2	AD	Variable onset glycogenosis renal tubular dysfunction

AR, autosomal recessive; AD, autosomal dominant; CHI, congenital hyperinsulinism; HI, hyperinsulinism

(2) Dominantly inherited K_{ATP}-CHI: Dominant K_{ATP}-CHI is caused by a monoallelic mutation in the K_{ATP} channel genes. The presentation is usually relatively milder, and patients often respond to diazoxide[29] although there are some refractory cases[30].

(3) Focal K_{ATP}-CHI:

i) Pathogenesis

In patients with focal K_{ATP}-CHI, abnormal β-cells are confined to a restricted region in the pancreas. In close proximity with the K_{ATP} channel genes at chromosome 11p15.1, an imprinted region at 11p15.5 harbors maternally expressed tumor suppressors, *H19* and *CDKN1c*, and a paternally expressed growth factor gene, *IGF2*. The focal lesion arises in an individual with a paternally inherited, monoallelic mutation in one of the K_{ATP} channel genes. When segmental paternal uniparental disomy occurs as a somatic mutation during the development of the pancreas, that particular cell loses K_{ATP} channel activity. At the same time, the tumor-suppressor activities of *H19* and *CDKN1C* are lost, and the activity of *IGF2* is doubled. This leads to a growth advantage for the abnormal β-cells and eventually leads to formation of a focal lesion[31-34]. Histologically, the focal lesion is characterized by the presence of large β-cells with enlarged nuclei similar to those of the diffuse lesion, and β-cells outside the focus have normal histology[35-37].

ii) Clinical implication

Although 96.2% of focal lesions are unresponsive to diazoxide[3], when the focal lesion is identified preoperatively, partial pancreatectomy can cure the patient without postoperative complications. Therefore, the identification and localization of focal lesions are extremely important. However, because they are generated during the normal organogenesis of the pancreas, they cannot usually be detected using conventional imaging modalities such as computed tomography (CT), magnetic resonance imaging, and angiography. The focal lesions can be preoperatively identified using molecular analysis and ^{18}F-fluoro-L-DOPA positron emission tomography (^{18}F-DOPA PET) scans, thereby enabling surgeons to plan the surgical procedure and to find the lesion intraoperatively.

iii) ^{18}F-DOPA PET scan

^{18}F-DOPA is incorporated into β-cells by DOPA-decarboxylase, which is abundant in β-cells. Following the initial description of its role in identifying the focal lesion[38], its usefulness has been reported in a number of publications[39,40]. ^{18}F-DOPA PET detects focal lesions as small as 5 mm and is better preformed as PET-CT. However, there are some challenges in interpreting the results. First, artifact uptakes tend to be found in the head of the pancreas because the head has a larger mass than the rest of the pancreas and because ^{18}F-DOPA is excreted into the bile duct. Second, ^{18}F-DOPA PET does not necessarily show the exact size of the lesion, especially when the lesion extends so-called tentacles out of the central lesion. These problems appeared more pronounced in our experience in Japan[41].

iv) Epidemiology of focal K_{ATP}-CHI

Previously, it was reported that approximately 40%–60% of surgically treated patients had focal CHI[31,42,43]. However, recent molecular analysis has revealed a racial disparity in the frequency of paternally inherited monoallelic mutation in K_{ATP}-CHI patients. For example, the percentage of patients with a paternally inherited monoallelic K_{ATP}-channel mutation is 20.6% in Spain[44], 33% in Norway[45], 84.2% in Japan[46], 37.7% in Germany[47], 58% in China[48], and 25% in the UK[27]. Obviously, these figures could be affected by ascertainment biases and by small sample sizes. In Japan, we have presently identified 46 patients with K_{ATP}-CHI, and 37 (80.4%) have paternal mutations. Therefore, combined with the report from China[48], it appears that Asians tend to have a higher frequency of paternally inherited mutation, suggesting the presence of focal CHI. The identification of focal CHI, therefore, is even more important for Asian patients.

v) Discordant molecular and ^{18}F-DOPA PET results

Not all patients with a paternally inherited K_{ATP} channel mutation have focal uptake by ^{18}F-DOPA PET, and some of these actually show diffuse histology. For example, Banerjee et al.[49] reported that 31% of patients with a paternal monoallelic mutation showed diffuse uptake on 18F-DOPA PET. Similarly, Kapoor et al.[27] reported that 26% of patients with paternal mutation appeared to have a diffuse lesion on PET. These results may indicate that not all maternal mutations were identified by the molecular analysis. However, when monoallelic mutations were identified in patients with K_{ATP}-CHI, the majority were paternal mutations: 79.3% and 65% in two UK series[27,49], 84.2% in Japan[46], and 83.3% in Norway[45]. Selectively missing the maternal allele during the molecular analysis is statistically highly unlikely. Another possibility, therefore, is that these patients have unusually scattered focal CHI that resembles true diffuse CHI. Further analysis is necessary to address this problem.

2) Non-K_{ATP} channel CHI

Most other persistent CHI are caused by excessive anaplerosis (replenishment of metabolic intermediate) into the GSIS pathway. With the exception of *GCK* and *SLC16A1* mutations, these non-K_{ATP}-channel CHI are usually responsive to diazoxide.

(1) GDH

GDH is encoded by *GLUD1* at chromosome 10q23.3. GDH mediates conversion of glutamate to α-ketoglutarate and ammonia, which is one of the major anaplerotic pathways in the Krebs cycle. An activating mutation in the *GLUD1* gene then supplies excess α-ketoglutarate into the Krebs cycle. The resulting overproduction of ATP causes CHI associated with hyperammonemia (hyperinsulinism–hyperammonemia syndrome)[50]. Both dominantly inherited and sporadic cases have been reported. Hypoglycemia is responsive to diazoxide, but hyperammonemia is resistant to conventional treatment.

Because GDH is allosterically activated by leucine, GDH-CHI presents with the typical leucine-sensitive CHI.

3) HADH

HADH—previously known as short-chain hydroxyacyl CoA dehydrogenase—is encoded by *HADH* at 4q22–q26. HADH functions in the mitochondrial matrix to catalyze the oxidation of straight-chain 3-hydroxyacyl-CoAs as part of the β-oxidation pathway. Unlike other proteins in the β-oxidation pathway, HADH is abundant in pancreatic β-cells and inhibits the activity of GDH. Biallelic HADH mutation then causes activation of GDH and hyperinsulinemia[51-53].

4) Glucokinase

Glucokinase is encoded by *GCK* at chromosome 7p15. Patients with GCK-HI have an activating mutation in *GCK*. This leads to overactivity in the GSIS pathway and oversecretion of insulin[54-56]. On the contrary, inactivating monoallelic mutation is a cause of MODY2 or GCK-MODY[57]. Recently, a somatic activating mutation in GCK has been proposed as a cause of a novel form of diazoxide-responsive focal CHI[58].

5) Uncoupling protein 2

Mitochondrial uncoupling protein 2 (UCP2) is encoded by *UCP2* at chromosome 11q13. UCP2 protein leaks protons across the inner mitochondrial membrane, thereby uncoupling the oxidative phosphorylation from ATP generation. Patients with a monoallelic mutation in UCP2 have excessive ATP production leading to HI[59].

6) Monocarboxylate transporter 1

Monocarboxylate transporter 1 (MCT1) encoded by *SLC16A1* at 1p12 is in the cell membrane and transports extracellular lactate and pyruvate into the cells. In pancreatic β-cells, the activity of MCT1 is normally suppressed to prevent lactate influx during exercise. In patients with exercise-induced HI, researchers identified mutations in the promoter of *SLC16A1* that activate the transporter. During exercise, extracellular lactate is fluxed into the β-cells and is converted to pyruvate, which fuels the GSIS pathway. The resulting increase in ATP production leads to HI[60].

3. Syndromic CHI

A variety of syndromes are reportedly associated with CHI. Because CHI is not a common feature of these syndromes, some of these associations may be coincidental. Nevertheless, CHI is frequently associated with Beckwith-Wiedemann syndrome, Sotos syndrome, Kabuki syndrome, Costello syndrome, mosaic Turner syndrome, or congenital deficiency of glycosylation[61]. In these syndromes, the association may have biological implications more than by-chance association. Of note is the Usher-CHI syndrome[62,63] in which CHI is associated with the symptoms of Usher syndrome, i.e., hearing loss and retinitis pigmentosa. This association is caused by biallelic deletions encompassing the K_{ATP} channel genes at 15p11 and the adjacent *USH1C* gene at 11p14.3, which is responsible for Usher syndrome.

Current treatment strategies

Current treatment strategies are summarized in Table 3 and are reviewed below.

1. Diazoxide

Diazoxide is a benzothiazine derivative that acts on the SUR1 subunit of the K_{ATP} channel, activating it. Diazoxide is used orally in three divided doses (5–15 mg/kg/day) and is effective for a variety of CHI subtypes[64]. However, it is generally ineffective for the most severe, neonatal-onset, recessive, and focal forms of K_{ATP}-CHI. Dominant K_{ATP} channel CHI often responds to diazoxide, although some unresponsive cases have been reported[32]. Hypertrichosis occurs in most patients and could be a serious concern. Other side effects include water retention, which could cause serious problems such as congestive heart failure or reopening of the ductus arteriosus[65,66]. This side effect may be of particular concern in patients with a low birth weight, as in transient CHI. Routine coadministration of diuretics is advised.

2. Octreotide

Octreotide is a somatostatin analog that acts on the somatostatin receptors SSTR2 and SSTR5 and inhibits secretion of a variety of hormones, including gastrin, cholecystokinin, glucagon, growth hormone, secretin, pancreatic polypeptide, thyroid stimulating hormone (TSH) vasoactive intestinal peptide, and insulin. Although its use for CHI has not been licensed in any country, it has been used for nearly 20 years for both short- and long-term control of diazoxide-unresponsive CHI[67,68]. It is administered as multiple daily subcutaneous injections (3–4 times/day) or by continuous subcutaneous infusions using an insulin pump. In our experience, many

Table 3. Treatment for congenital hyperinsulinism

Nutritional
Hypertonic glucose infusion
Cornstarch
Glycogen storage disorder formula
Enteral feeding (nasogastric tube feeding, gastrostomy)
Medical
Diazoxide, 5–20 mg/kg/day, po
Nifedipine, 0.25–2.5 mg/kg/day, po
Octreotide, 5–25 μg/kg/day, sc
Glucagon, 1–20 μg/kg/hr, sc, iv, im
Surgical
Pancreatectomy (partial, subtotal, neartotal)

po, per oral; sc, subcutanetous; iv, intravenous; im, intramuscular.

patients with K_{ATP} channel CHI can be maintained on long-term treatment until spontaneous remission at 2–5 years of age[69]. Common adverse events include gastrointestinal symptoms, white stool, dilated gall bladder with or without gall stones, and growth deceleration after 2 years of age. Rarer, but more serious side effects, include hepatitis[70], necrotizing enterocolitis[71] and long QT syndrome[72].

3. Glucagon

Glucagon stimulates glycogenolysis and gluconeogenesis to increase hepatic glucose output. It is administered by intravenous, subcutaneous, or intramuscular routes, and has been used mainly for short-term control of diazoxide-unresponsive patients who are not adequately controlled by other means. However, as is the case for octreotide, its long-term use until spontaneous remission has been reported[73,74]. Apart from its gastrointestinal side effects, its crystallization in the infusion tubes has been a major practical problem during long-term use. Part of this problem may be ameliorated by the development of a water-soluble formulation that is in a phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT01972152).

4. Pancreatectomy

When patients are not responsive to medical treatment and cannot be weaned off treatment with intravenous glucose infusions, pancreatectomy should be considered. When a focal lesion is identified preoperatively, partial pancreatectomy is the treatment of choice. However, the lesion is not always visible or palpable at the site indicated by ^{18}F-DOPA PET. Although intraoperative sonography can aid in identification[75], repeated intraoperative biopsy may be necessary to help surgeons determine the extent of pancreatectomy. Such a treatment is made possible only by a multidisciplinary team composed of surgeons, radiologists, pediatric endocrinologists, and pathologists who are well experienced in the treatment of CHI[76,77]. When a focal lesion is identified in the body or tail of the pancreas using ^{18}F-DOPA PET, resection is relatively easy; even if the exact location of the focal lesion cannot be identified, distal pancreatectomy of <70% typically cures the patient without a risk of postoperative diabetes. On the contrary, when the lesion is identified in the head of the pancreas, resection may be difficult without damaging important adjacent structures such as the main pancreatic duct or the common bile duct. In those cases, pancreatic head resection with Roux-en-Y reconstruction of distal pancreatojejunostomy has been proposed[78]. For patients with diazoxide-unresponsive diffuse CHI, extended resection of the pancreas is still needed. Even in these cases, near-total pancreatectomy should be avoided as much as possible in order to reduce the development of postsurgical diabetes[79,80]. A 70%–90% resection may be considered to reduce the pancreatic mass and to facilitate medical management.

Other unsolved questions and future perspectives

1. Causes of the remaining 50% of persistent CHI

At present, even with the most comprehensive molecular analysis, mutations in known causative genes cannot be identified in 21.3% of patients[26]. When confined to diazoxide-responsive cases, mutations are not identified in 53%. Therefore, if we assume that all persistent CHI is genetic in origin, there must be unidentified causative genes. In an effort to address this issue, Proverbio et al.[81] analyzed 17 families with CHI who lacked mutations in *ABCC8/KCNJ11* using a combination of transmission disequilibrium tests and whole-exome sequencing and reported 21 novel genes as possible candidates. Although none of these have been confirmed as causative, further efforts employing next-generation sequencing may answer these questions.

Using next-generation sequencing, Flanagan et al.[82] took a different approach of sequencing the entire genomic region of the *ABCC8* and *HADH* genes[82]. By this strategy, they identified deep intronic mutations of both genes causing CHI, c.1333-1013A>G in *ABCC8* and c.636þ471G>T *HADH*. Surprisingly, these mutations were common in the Irish and Turkish populations, accounting for 14% of focal hyperinsulinism cases and 32% of subjects with HADH mutations.

2. Causes of transient CHI (a hypothesis)

Transient CHI is common in infants who were born small for their gestational ages (SGA) or in those with perinatal stress. However, little is known about its cause. SGA infants are in a hypoxemic condition in utero[83]. Because β-cell function is inhibited by hypoxia-inducible factor 1α (HIF1α)[84,85], a sudden increase in the oxygen tension at delivery may downregulate HIF1α leading to hyperinsulinemia. In line with the observation that oxygenation of fetal blood improves with gestational ages[83], it has been reported that blood insulin levels at birth correlate with the gestational age of the infants: 9.2 μIU/mL for full term; 10.3 μIU/mL for early term; 13.2 μIU/mL for late preterm; and 18.9 μIU/mL for early preterm[86]. Hyperinsulinemia at birth, therefore, is a common finding in newborns with a lower birth weight.

3. Mechanism of spontaneous remission of CHI

Both diffuse and focal HI resolve spontaneously over time[87]. A previously proposed mechanism for spontaneous remission of CHI is apoptotic death of insulin-oversecreting β-cells[88]. However, the initial event could be functional shutdown of insulin secretion rather than apoptotic cell death because the abnormal β-cells could still be observed by ^{18}F-DOPA PET at an early stage of the spontaneous remission of focal K_{ATP}-CHI[89]. Manipulating the process of functional shutoff could be an

attractive treatment option for CHI.

4. Novel medications for diazoxide–unresponsive CHI

1) Novel somatostatin analogues

Novel somtatostatin analogues have been successfully used for CHI or other forms of HI, including lanreotide[90,91] or long-acting octreotide[92] for CHI. In addition, pasireotide has been tested for severe postgastric bypass HI[93]. Although octreotide and lanreotide have affinities for somatostatin receptors SSTR2 and SSTR5, pasireotide has a broader spectrum of activity for other types of SSTRs[94].

2) Small molecule corrector of K_{ATP}-channel CHI

The search for small molecules to treat CHI is fueled by previous efforts to correct the trafficking defect of the cystic fibrosis transmembrane conductance regulator, which is deficient in patients with cystic fibrosis. The idea is to use small molecules as pharmacological chaperones to correct the trafficking defect and help their expression to the cell surface[95]. This strategy is applicable to certain mutations of the K_{ATP}-channel genes. Thus far, sulfonylureas[96] and carbamazepine[77] have been successfully used to correct the trafficking defects of mutations within the transmembrane domains 0 and 1 (TMD0, TMD1) of *ABCC8*.

3) Glucagon-like peptide 1 (GLP1) receptor antagonist

GLP1 is secreted from the L-cells of the small intestine and binds to the GLP1 receptors in pancreatic β-cells, thereby stimulating the secretion of insulin (the incretin pathway). This pathway has a role in the amplification of postprandial insulin secretion and has been the target of novel treatments for type 2 diabetes. An antagonist of the GLP1 receptor, exendin[9-39], has been shown to be effective for the treatment of CHI in an open-label, randomized clinical trial[98]. Although the effect was not complete, and monotherapy of CHI with this class of medication appears impractical, GLP1 receptor antagonists may have a role in adjunctive treatment of CHI.

4) Mammalian target of rapamycin (mTOR) inhibitors

mTOR is a member of the serine/threonine kinase family and is induced by amino acids (arginine and branched-chain amino acids), stress, high-energy status, oxygen, and growth factors. mTOR is complexed with regulatory-associated protein of mTOR (Raptor), mammalian LST8/G-protein β-subunit–like protein (mLST8/GβL), PRAS40, and DEPTOR to form the mTORC1 complex. Alternatively, mTOR is complexed with mLST8/Gβ, rapamycin-insensitive companion of mTOR (Rictor), and mammalian stress-activated protein kinase-interacting protein 1 (mSIN1) to form mTORC2 and is active in a variety of cellular mechanisms, including protein synthesis, cell proliferation, or cell survival. Therefore, mTOR inhibitors have been widely used to treat neoplasms. In terms of glucose metabolism, activation of mTORC1 is known to cause increased glucose uptake and glycolysis via HIF1. In addition, mTORC2 is known to play an important role in maintaining the β-cell mass through the phosphotidylinositol-3-kinase/mTORC2/AKT signaling pathway[99]. Sirolimus, one of the mTOR inhibitors, was successfully used to treat patients with diazoxide unresponsive CHI[100]. These classes of medications therefore may have a role in the treatment of CHI as well.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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