PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2014) **56**, 467–476 doi: 10.1111/ped.12390

Review Article

Congenital hyperinsulinism: Global and Japanese perspectives

Tohru Yorifuji,[1,2,3] Michiya Masue[4] and Hironori Nishibori[5]

[1]*Pediatric Endocrinology and Metabolism, Children's Medical Center,* [2]*Clinical Research Center,* [3]*Department of Genetic Medicine, Osaka City General Hospital, Osaka, Departments of* [4]*Pediatrics and* [5]*Radiology, Kizawa Memorial Hospital, Gifu, Japan*

Abstract Over the past 20 years, there has been remarkable progress in the diagnosis and treatment of congenital hyperinsulinism (CHI). These advances have been supported by the understanding of the molecular mechanism and the development of diagnostic modalities to identify the focal form of ATP-sensitive potassium channel CHI. Many patients with diazoxide-unresponsive focal CHI have been cured by partial pancreatectomy without developing postsurgical diabetes mellitus. Important novel findings on the genetic basis of the other forms of CHI have also been obtained, and several novel medical treatments have been explored. However, the management of patients with CHI is still far from ideal. First, state-of-the-art treatment is not widely available worldwide. Second, it appears that the management strategy needs to be adjusted according to the patient's ethnic group. Third, optimal management of patients with the diazoxide-unresponsive, diffuse form of CHI is still insufficient and requires further improvement. In this review, we describe the current landscape of this disorder, discuss the racial disparity of CHI using Japanese patients as an example, and briefly note unanswered questions and unmet needs that should be addressed in the near future.

Key words 18F-dihydroxyphenylalanine, congenital hyperinsulinism, potassium channel.

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in neonates and infants before weaning. Other terms for CHI, such as "nesidioblastosis" or "persistent hyperinsulinemic hypoglycemia in infancy," are currently less frequently used. "Nesidioblastosis" is a pathological term indicating the continuous proliferation of islet cells from the pancreatic ducts, which is a common finding in healthy newborns and in obese subjects,[1–4] and the term "persistent hyperinsulinemic hypoglycemia in infancy" is no longer favored because symptoms of CHI could develop after infancy or even in adulthood.[5]

Persistent severe hypoglycemia could lead to permanent brain damage, so appropriate and timely treatment is extremely important for the prognosis of patients with CHI.[6–9] Patients resistant to medical treatment previously often underwent near-total pancreatectomy, which involves removal of more than 95% of the total volume of the pancreas. The results, however, were frequently unsatisfactory because many patients remained hypoglycemic after surgery and most patients without hypoglycemia eventually developed postsurgical insulin-dependent diabetes mellitus.[9–11]

Fortunately, during the past decade, there has been major progress in the understanding and treatment of CHI, and many cases are now curable without postsurgical complications. However, there are still unanswered questions about the cause of CHI and unmet needs of patients that need to be addressed. Importantly, current diagnostic and therapeutic strategies are not uniformly available and applicable throughout the world.

We have studied CHI in Japan over the past several years and found that there are regional biological and social differences in this disorder from what has been reported globally. In this review, we describe the current global landscape of CHI and discuss an example of CHI in Japan that differs from the global trend.

Mechanism of glucose-induced insulin secretion

Glucose-induced insulin secretion

To facilitate the understanding of the pathophysiology of CHI (Fig. 1), the following is a brief summary of the pathway of glucose-induced insulin secretion. After a meal, blood glucose is at an elevated level and is transported into the cells by glucose transporters. The transporter for the pancreas is glucose transporter 2 (GLUT2), which has a low affinity and high capacity for glucose, galactose, or fructose and transports them within the range of physiological concentrations.[12] The transported glucose is then phosphorylated by glucokinase, a member of the hexokinases. This enzyme has a low affinity for glucose and is not inhibited by its end product, glucose-6-phosphate. Therefore, it generates glucose-6-phosphate in a wide range of physiological glucose concentrations and is considered the glucose sensor of the pancreas.[13] Glucose-6-phosphate is metabolized through glycolysis to form pyruvate, which is then transported into mitochondria. Within mitochondria, pyruvate is further metabolized through the Krebs cycle and the oxidative phosphorylation

Correspondence: Tohru Yorifuji, MD PhD, Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, 2-13-22 Miyakojima-Hondori, Miyakojima, Osaka 534-0021, Japan. Email: t-yorifuji@hospital.city.osaka.jp

Received 11 March 2014; accepted 12 May 2014.

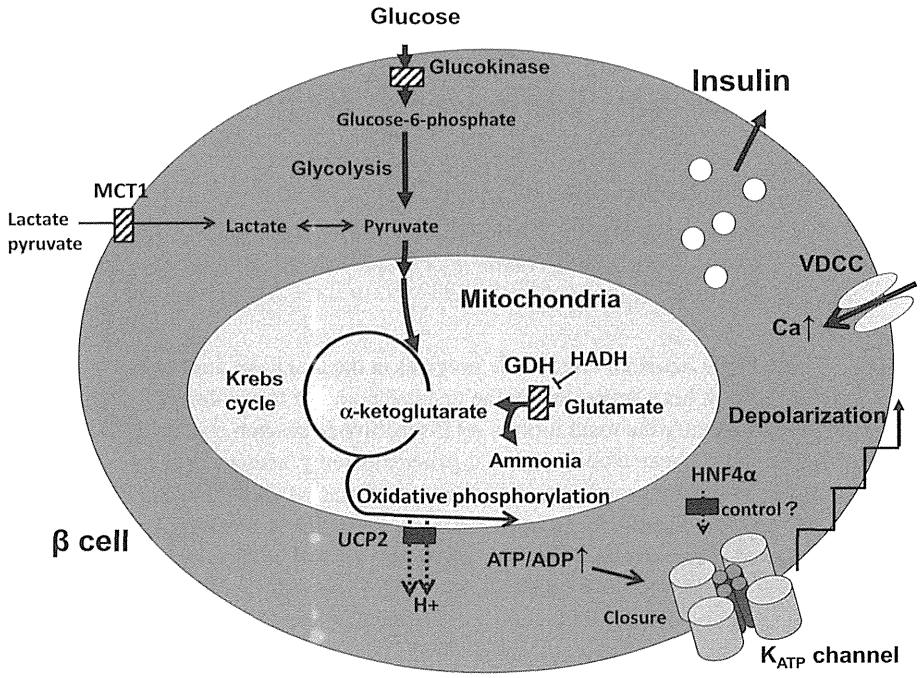

Fig. 1 Glucose-induced insulin secretion pathway is shown together with molecules relevant to congenital hyperinsulinism. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GDH, glucose dehydrogenase; HADH, L-3-hydroxyacyl-coenzyme A dehydrogenase; HNF4α, hepatocyte nuclear factor 4α; K_{ATP} channel, adenosine triphosphate–sensitive potassium channel; MCT1, monocarboxylate transporter 1; UCP2, uncoupling protein 2; VDCC, voltage-dependent calcium channel.

pathway. During this process, one molecule of glucose generates 38 molecules of adenosine triphosphate (ATP). The increased intracellular ATP/adenosine diphosphate (ADP) ratio then leads to the closure of the ATP-sensitive potassium channel (K_{ATP} channel) in the cell membrane, which prevents the potassium current through the channel and causes depolarization of the cell membrane. The change in the membrane potential opens the voltage-gated calcium channel, leading to influx of extracellular calcium into the cells. The increased intracellular calcium concentration then facilitates exocytosis of the insulin-containing vesicles and secretion of insulin.[14]

K_{ATP} channel

The K_{ATP} channel is an octameric structure composed of four molecules of Kir6.2 subunits, which form the inner pore, and surrounded by four molecules of SUR1 subunits, which control the channel activity. Increased levels of intracellular ATP are sensed by the Kir6.2 subunits to limit the channel current. In contrast, increased Mg-ADP is sensed by the SUR1 subunits to increase the channel current. Therefore, an increased ATP/ADP ratio leads to a decreased open probability of the channel leading to secretion of insulin.[14,15]

Diagnosis of CHI

CHI is diagnosed on the basis of inappropriately elevated serum insulin levels in the presence of hypoglycemia. However, it is difficult to set distinct cut-offs for diagnosis. First, there are no confirmed age-dependent cut-offs for the diagnosis of hypoglycemia. Traditionally, blood glucose levels < 2.5 mmol/L (45 mg/dL) in children and <3.0 mmol/L (54 mg/dL) in adults have been widely accepted as cut-offs for hypoglycemia. These cut-offs were derived from physiological responses against hypoglycemia,[16] but they should probably differ depending on the clinical status of the individual patient.[17] Second, the cut-off for an "inappropriately high" insulin level is also unknown. A serum insulin level of >3 μU/mL in the presence of hypoglycemia is probably sufficient to diagnose hyperinsulinism. However, not all "detectable insulin" in the presence of hypoglycemia indicates a diagnosis of hyperinsulinism but instead depends on other factors, such as the assay sensitivity or the state of insulin resistance. To circumvent these difficulties, criteria such as the need for a higher glucose infusion to maintain euglycemia or the response to glucagon injections, are also used as adjuncts to help diagnose hyperinsulinism.[18] Table 1 shows the diagnostic criteria for hyperinsulinemic hypoglycemia proposed as a diagnostic guideline by a workgroup from the Japanese Society for Pediatric Endocrinology (http://jspe.umin.jp/).

Table 1 Diagnostic criteria for hyperinsulinemic hypoglycemia from the Japanese Society for Pediatric Endocrinology

Laboratory data during hypoglycemia (critical sample):
Blood insulin level >2–5 μIU/mL
Blood free fatty acid level <1.5 mmol/L
Blood β-hydroxybutyrate level <2.0 mmol/L
Glucose infusion rate to maintain normoglycemia:
>6–8 mg/kg/min

Epidemiology of transient and persistent CHI

Transient and persistent CHI

CHI can be categorized as: transient CHI, which develops soon after birth and usually resolves within the first 3–4 weeks of life; and persistent CHI, which could develop later and lasts longer.

Epidemiology

Persistent CHI

The incidence of persistent CHI has been reported to be approximately one case per 50 000 live births worldwide[19] but appears to vary depending on the gene frequency of mutant alleles and the marital habitus of the particular population. In 2009, we conducted a national survey to explore the epidemiological and treatment status of CHI in Japan; the results showed that the incidence of persistent CHI was one case per 35 400 live births.[20] In Saudi Arabia, where consanguineous marriage is more common, the incidence of CHI is reported to be much higher at one case per 2675 live births.[21]

Transient CHI

The incidence of transient CHI appears to be much higher than that for persistent CHI. The estimated incidence of transient CHI in Japan has been reported to be twice as high as that of persistent CHI at one case per 17 000 live births.[20] However, the incidence is probably underestimated because milder transient CHI that resolves within 1 week with a glucose drip infusion is probably not diagnosed or reported properly.

Differentiation of transient and persistent CHI

In the aforementioned survey in Japan, we identified 61 patients with persistent CHI and 127 patients with transient CHI who were born between 2007 and 2009.[20] Interestingly, the only clinical indices that could differentiate transient from persistent CHI were shorter gestational age and lower birthweight SDS in the transient CHI group. No other parameters, such as insulin/glucose ratio, total ketone bodies, or total free fatty acid levels, could differentiate these two groups with statistical significance.

Transient and persistent CHI: Known causes

Transient CHI

The known causes of CHI are listed in Table 2. Transient CHI is believed to be caused mostly by non-genetic factors, such as low birthweight or a stressful perinatal period. Important exceptions are monoallelic mutations in the *HNF4A* gene[22–25] and possibly the *HNF1A* gene.[26] Both of these genes code for transcription factors, which stimulate transcription of a variety of genes in the pancreatic β cells and the hepatocytes. Mutations in these genes have been shown to cause forms of dominantly inherited monogenic diabetes, maturity-onset diabetes of the young types 1 and 3, respectively. Exactly how mutations in these genes cause transient CHI is currently unknown. However, recent findings indicate the presence of gene–gene interaction between the *HNF4A* and *KCNJ11* genes.[27] The presentation of hyperinsulinism related to an *HNF1A* mutation appears to be different from that of typical transient CHI in that the patient could develop hypoglycemia later in infancy or in childhood.[26] Patients with *HNF4A* or *HNF1A* mutations could develop diabetes mellitus later in life and therefore should be followed up after remission of hypoglycemia.

Persistent CHI

In contrast to transient CHI, most cases of persistent CHI are believed to be caused by genetic factors; however, causative gene mutations have been identified in only 45.3–79% of patients.[28,29]

Table 2 Known causes of congenital hyperinsulinism

Persistent	Nonsyndromic	K_{ATP} channel genes	AR, AD, focal (monoallelic paternal + paternal uniparental disomy)
		ABCC8 (SUR1)	
		KCNJ11 (Kir6.2)	
		GLUD1 (glutamate dehydrogenase)	AD, hyperammonemia
		GCK (glucokinase)	AD, focal?
		HADH (L-3-hydroxyacyl-coenzyme A dehydrogenase)	AR
		UCP2 (uncoupling protein 2)	AD
		INSR (insulin receptor)	AD
		SLC16A1 (monocarboxylate transporter 1)	AD
	Syndromic	*ABCC8, KCNJ11, USH1C*: Usher-CHI syndrome	AR
		Beckwith–Wiedemann syndrome	
		Congenital deficiency of glycosylation 1a, 1b, 1c	AR
		Kabuki syndrome	AD
		Mosaic Turner syndrome	
		Other	
Transient		Infant of diabetic mother	
		Small for gestational age	
		Stress-induced	
		Maternal medication (e.g. ritodrine hydrochloride)	
		HNF4A	AD
		HNF1A	AD

AD, autosomal dominant; AR, autosomal recessive.

Genetic causes of persistent CHI

K_{ATP} channel CHI. The most commonly known genetic cause of persistent CHI is in activating mutations in the K_{ATP} channel genes, *KCNJ11* and *ABCC8*.[30–32] Although the overall mutation detection rate for persistent CHI is slightly more than 50%, when confined to diazoxide-unresponsive cases, mutations in the K_{ATP} channel genes could be identified in 87.6–91% of cases.[28,29]

The mode of inheritance of K_{ATP} channel CHI could be both autosomal dominant and recessive. In addition, a specific mode of paternally inherited monoallelic mutation leading to the focal form of CHI is known. In general, recessively inherited K_{ATP} channel CHI presents with a more severe phenotype that is unresponsive to diazoxide, often necessitating near-total pancreatectomy.[30,33] In contrast, dominantly inherited K_{ATP} channel CHI presents with a milder phenotype, is mostly responsive to diazoxide, and rarely requires pancreatectomy.[34–37] It is generally assumed that the dominantly inherited form is relatively rare compared with the recessive form, but this could be an underestimate because mild dominant CHI may go unrecognized clinically. Pathological features of recessive K_{ATP} channel CHI include the presence of enlarged islet cell nuclei throughout the pancreas.[3,38–42] Basically, all β cells in the pancreas are abnormal in both recessive and dominantly inherited forms (diffuse lesion).

Usher-CHI syndrome. Usher-CHI syndrome is a specific form of recessively inherited K_{ATP} channel CHI. The *USH1C* gene is located at chromosome 11p15.1, with close proximity to the K_{ATP} channel genes, and is responsible for Usher syndrome. Usher-CHI syndrome is caused by the homozygous deletion spanning the *USH1C* gene and the K_{ATP} channel genes and is characterized by CHI associated with hearing loss and retinal degeneration.[43,44]

Focal form of K_{ATP} channel CHI

In contrast to the recessive and dominant forms of K_{ATP} channel CHI, the focal form of CHI is distinct in that abnormal β cells are confined to a restricted area of the pancreas. This is of enormous clinical significance because if the focal lesion is identified and localized before surgery, the patient can be cured of hypoglycemia by partial pancreatectomy without postoperative complications (see the section on "Treatment strategies for CHI" below).

The focal form of CHI occurs in patients who have a paternally inherited monoallelic mutation in one of the K_{ATP} channel genes.[45,46] Adjacent to the K_{ATP} channel genes at chromosome 11p15.1, there is a cluster of imprinted genes, *H19, IGF2*, and *CDKN1C*, at 11p15.5. *H19* and *CDKN1C* are tumor suppressor genes expressed exclusively from the maternal allele, whereas *IGF2* is a growth factor gene expressed from the paternal allele. When segmental paternal uniparental disomy occurs as a somatic event during the development of the pancreas in a person with a paternally inherited K_{ATP} channel mutation, that particular cell loses the K_{ATP} channel activity. In addition, the cell loses the tumor suppressor activity of H19 and CDKN1C and receives a double dose of IGF2, leading to a growth advantage during embryogenesis that eventually results in the formation of a focal lesion of insulin-overproducing cells.[45,46] The focal lesions are usually up to 1 cm in size, although a giant focal lesion that covers almost the whole pancreas has been reported.[47] The boundaries of the focal lesion, however, are often not very clearly demarcated because of the presence of numerous "tentacles" extending from the main lesion. Unfortunately, unlike insulinomas, these lesions are usually not identifiable by conventional imaging modalities, such as computed tomography, magnetic resonance imaging, or angiography.

18F-fluoro-L-dihydroxyphenylalanine positron emission tomography

Together with the molecular diagnosis of a paternally inherited mutation, the development of an imaging modality, 18F-fluoro-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET), to localize the focal lesion has changed the management of patients with CHI.[48–53] 18F-DOPA is incorporated into the focal lesion by the action of DOPA decarboxylase, which is abundant in pancreatic β cells. Although an artifact in the head of the pancreas is often caused by the large size of the head and the excretion of 18F-DOPA in the common bile duct, 18F-DOPA PET has generally been reported to be very sensitive and could detect lesions as small as 5 mm.[48]

Other genetic causes of persistent CHI

Glutamate dehydrogenase. An activating mutation in the *GLUD1* gene that codes for glutamate dehydrogenase (GDH) causes a syndrome of CHI associated with hyperammonemia (HIHA syndrome).[54] GDH is an enzyme that catalyzes the conversion of glutamate to α-ketoglutarate and ammonia. Overproduction of α-ketoglutarate, a metabolic intermediate in the Krebs cycle, leads to an increased ATP/ADP ratio and to K_{ATP} channel-mediated oversecretion of insulin, while overproduction of ammonia leads to hyperammonemia. Because GDH receives a positive allosteric activation by leucine and ADP, the syndrome presents with classic leucine-sensitive hypoglycemia and responds well to diazoxide. Hyperammonemia is usually moderate (between 100 and 200 μg/dL) and is unresponsive to dietary protein restriction or other measures to decrease the production of ammonia in the intestines.

L-3-hydroxyacyl-coenzyme A dehydrogenase. The *HADH* gene codes for the enzyme L-3-hydroxyacyl-coenzyme A dehydrogenase (HADH), which was previously known as short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD). The mitochondrial enzyme catalyzes the penultimate step in the β-oxidation of fatty acids to its corresponding 3-ketoacyl CoA. Unlike other enzymes in the β-oxidation pathway, HADH is known to be abundant in pancreatic β cells and interacts directly with GDH to inhibit activity.[55] Therefore, recessively inherited biallelic-inactivating mutations in HADH lead to overactivity of GDH and hyperinsulinism.[55,56] Unlike HIHA syndrome, hyperammonemia is not a feature of HADH deficiency, probably because HADH is not abundant in other cell types that generate ammonia. HADH deficiency is the most common cause of

recessively inherited CHI and could increase urinary 3-hydroxyglutarate and plasma 3-hydroxybutyryl-carnitine levels. However, urinary organic acid analysis and serum carnitine profiles are often normal in these patients. Therefore, molecular analysis should be considered in patients who have diazoxide-responsive CHI and present with recessive inheritance.[57]

Glucokinase. The *GCK* gene codes for glucokinase, which phosphorylates glucose to form glucose-6-phosphate on entry into pancreatic β cells. Because glucokinase serves as a glucose sensor, an activating mutation in this gene causes overproduction of glucose-6-phosphate, which leads to activation of the glucose-induced insulin secretion pathway and oversecretion of insulin.[58–65] The clinical phenotype varies from mild, diazoxide-responsive cases to severe, medically unresponsive cases. Glucokinase could also be a cause of adult hyperinsulinism or postprandial hyperinsulinism.[61] Recently, a novel type of focal CHI presumably caused by a somatic mutation of glucokinase has been reported.[66]

Uncoupling protein 2. The *UCP2* gene codes for mitochondrial uncoupling protein 2 (UCP2), which is ubiquitously expressed in a variety of cell types, including pancreatic β cells, and leaks protons across the inner mitochondrial membrane, thereby uncoupling oxidative phosphorylation from ATP generation. A monoallelic inactivating mutation therefore leads to excess ATP generation and oversecretion of insulin.[67]

Monocarboxylate transporter 1. The *SLC16A1* gene codes for monocarboxylate transporter 1 (MCT1), which mediates the transport of lactate and pyruvate across cell membranes. In patients with exercise-induced hyperinsulinemic hypoglycemia, mutations in the promoter region of this gene have been identified.[68,69] These mutations have been shown to activate the promoter in pancreatic β cells, where MCT1 is normally underexpressed. This leads to the influx of lactate into β cells, when serum levels of lactate are elevated during exercise. Lactate and pyruvate are further metabolized to generate ATP, which leads to oversecretion of insulin through the glucose-induced insulin secretion pathway.

Treatment strategies for CHI

Table 3 shows the current treatment options for patients with CHI. In addition to nutritional support, including continuous intravenous glucose infusion, nasogastric feeding, or gastrostomy, the following medical and surgical treatments have been used.

Diazoxide

Diazoxide binds to the SUR1 subunit of the K_{ATP} channel and keeps the channel in an open state, thereby inhibiting glucose-induced insulin secretion. This medication has been used extensively in patients with CHI and is considered to be the first choice for treatment of all types of CHI.[70] It is effective for a variety of subtypes of CHI; however, unfortunately, it is usually ineffective for the most severe forms of neonatal-onset, K_{ATP} channel hyperinsulinism.[9,71] Except for water retention and hypertrichosis, diazoxide has relatively few adverse effects. However, it should be used in smaller infants with caution because water retention could lead to reopening of the ductus arteriosus or heart failure, especially when given without diuretics.[72]

Table 3 Current treatment modalities for congenital hyperinsulinism

Nutritional	Hypertonic intravenous glucose infusion
	Cornstarch, frequent feeding, nasogastric tube feeding, gastrostomy
Medications	Diazoxide
	5–20 mg/kg/day oral
	Nifedipine
	0.25–2.5 mg/kg/day oral
	Octreotide
	5–25 μg/kg/day subcutaneous
	Glucagon
	1–20 μg/kg/h subcutaneous, intravenous
Surgery	Pancreatectomy (partial, subtotal, near total)

Octreotide and other somatostatin analogues

Octreotide

Octreotide is a long-acting somatostatin analogue that binds to 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, vasoactive intestinal peptide, and insulin. The use of octreotide for the treatment of patients with CHI was first reported nearly 20 years ago.[73,74] Octreotide has been widely used and is effective for the treatment of patients with diazoxide-unresponsive CHI at least to some extent, and often patients can discontinue intravenous administration of glucose. In addition to short-term use before pancreatectomy, long-term subcutaneous administration of octreotide often leads to spontaneous remission of K_{ATP} channel CHI without surgery.[75] Common adverse events include gastrointestinal disturbances, especially at the initiation of treatment, and a dilated gallbladder with or without gallstones, biliary sludge, or white stool. In addition, rare but more serious adverse events, such as necrotizing enterocolitis[76] and hepatitis,[77–79] have been reported. Despite its usefulness, the use of octreotide for the treatment of patients with CHI is not licensed in any country, including Japan. A government-funded clinical trial to prove the efficacy and safety of octreotide is currently underway in Japan (UMIN Clinical Trials Registry, UMIN000012620, SCORCH study).

Other somatostatin analogues

On the basis of the same treatment strategy, successful use of other somatostatin analogues for the treatment of patients with hyperinsulinemic hypoglycemia has been reported, including long-acting octreotide,[80] lanreotide,[81,82] and pasireotide.[83] These medications have the advantages of a longer duration of activity (long-acting analogues) or activities for a broader range of somatostatin receptors (pasireotide). However, because of limited experiences, their efficacy and adverse event profiles are not currently clear.

Glucagon

Glucagon is a 29-amino acid peptide that is produced by the α cells of the islets. It is one of the counterregulatory hormones and acts by stimulating glycogenolysis and gluconeogenesis from the liver. Although it can be administered by subcutaneous or intramuscular injection, continuous intravenous administration is the most frequent route for patients with CHI who do not respond to treatment with diazoxide or octreotide. Traditionally, the use of glucagon for CHI has been limited to preoperative short-term use because of frequent crystallization within the route of administration. Recently, however, successful long-term subcutaneous use has been reported.[84,85]

Pancreatectomy

Decades ago, before the identification of the focal form of CHI, subtotal or near-total pancreatectomy was the treatment of choice for medically unresponsive patients with CHI. The consequences were often unsatisfactory, with many patients experiencing residual hypoglycemia or frequent occurrence of postoperative insulin dependent diabetes mellitus.[9,10] Currently, however, when we identify a focal form of CHI preoperatively by 18F-DOPA PET scan, the patient can potentially be cured by partial pancreatectomy without developing postoperative diabetes. However, there are several difficulties with this approach. First, even if we could identify the localization of the lesion by PET scan, the lesion is not always visible or palpable. Intraoperative ultrasonography sometimes helps to identify the lesion,[86] but extensive intraoperative biopsies are usually needed to identify the lesion and determine the extent of pancreatectomy.[40] Second, the localization of the focal lesion often poses surgical problems. When the lesion is in the tail or body of the pancreas, the surgery is straightforward. The patient could be cured by either enucleation of the lesion or distal pancreatectomy without developing postoperative diabetes. However, if the lesion is in the head of the pancreas and close to other structures, such as the main pancreatic duct or the common bile duct, damage to those structures must be avoided. When the lesion cannot be safely enucleated, pancreatic head resection and Roux-en-Y pancreaticojejunostomy is the proposed procedure of choice[87,88] but is a major operation and not without postoperative complications.[89] When the patient's condition could be maintained without intravenous administration of glucose, long-term medical treatment with octreotide or glucagon appears to be an alternative approach worth considering.[75,84]

Global and Japanese perspectives on CHI

Global trends in the management of CHI

Focal CHI

Identification and localization of focal CHI using 18F-DOPA PET and subsequent partial pancreatectomy appear to be the global standard, but this multidisciplinary approach is possible only where the medical resources are available.[90]

Diffuse CHI

Even today, the management of diazoxide-unresponsive diffuse CHI is not straightforward. The global trend is to avoid near-total pancreatectomy as much as possible because the incidence of postsurgical diabetes is high[9,10] and the outcome is unpredictable.[89,91] Fewer patients are undergoing near-total pancreatectomy than before,[9] and even when pancreatectomy is necessary, often the goal is to make medical treatment easier by reducing the mass of abnormal β cells.

Japanese perspectives

Although the established global standard for the management of CHI basically holds true for Japanese patients, there are several important disparities from both medical and social standpoints.

Different molecular background of CHI

Previous reports from Israel and France showed that approximately 40% of patients with surgically treated CHI had focal lesions.[92,93] However, according to recent molecular analyses of patients with K_{ATP} channel CHI, there appears to be racial disparity in the molecular background. For example, reports from a German registry showed that 38% of patients with K_{ATP} channel CHI had paternally inherited monoallelic mutations, thus suggesting the presence of a focal lesion.[94] Similar studies from other countries have reported different figures; in the UK,[29] Italy,[95] and China,[96] paternal monoallelic mutations were found in 25%, 54%, and 58% of patients with K_{ATP} channel CHI, respectively. We previously reported that 84.2% of Japanese patients with K_{ATP} channel CHI had paternal monoallelic mutations;[97] at the time of this writing, we have completed molecular analyses on 130 Japanese patients with CHI and found that 80.4% of patients with K_{ATP} channel CHI had paternal mutations. It is known that not all patients with a paternal mutation have a focal lesion,[98,99] but it appears that identification of focal CHI is even more important for Japanese patients.

Different accuracy of 18F-DOPA PET

Previous reports have repeatedly shown the efficacy of 18F-DOPA PET in localizing focal CHI.[48–53] Our experiences in Japan have demonstrated that the procedure is also useful for localization of the lesions. However, in Japanese patients, the interpretation of the results is often difficult because a focal lesion may resemble a diffuse lesion or a multifocal lesion.[100] The reason for this discrepancy is not known currently. Our impression is that the symptoms of patients with focal lesions often appear to be milder compared with previously reported clinical scenarios in Caucasian patients, which might be reflected by the lower uptake of 18F-DOPA in Japanese patients. In fact, in our experiences with 18F-DOPA PET imaging in Caucasian patients, most of these patients had greater uptake in terms of standardized uptake value compared with Japanese patients.

Different management strategy for focal CHI in the head of the pancreas

As described previously, focal lesions in the head of the pancreas are not easy to enucleate. The proposed treatment strategy for those lesions is pancreatic head resection and Roux-en-Y pancreaticojejunostomy.[87,88] Because this is major surgery with possible postoperative complications, pediatric surgeons and

caregivers are not always enthusiastic about performing this procedure. Combined with the fact that focal lesions in Japanese patients appear to be less aggressive and could be relatively easily controlled by continuous subcutaneous infusion of octreotide, when we cannot safely enucleate the lesions in the head of the pancreas, we often choose to continue medical treatment without pursuing the instant cure of the disease.[75] Many of these patients could later be weaned off treatment with spontaneous remission of the disease.

Resources to achieve optimal multidisciplinary treatment

For state-of-the-art treatment of CHI, a team consisting of experienced pediatric endocrinologists, radiologists, pathologists, and surgeons is necessary. In addition, 18F-DOPA PET and a molecular diagnostic laboratory must be available. It is not easy to fulfill these requirements, especially in developing countries. In Japan, the authors' facilities are virtually the only ones to currently offer molecular diagnostic services and 18F-DOPA PET scans. Surgical and medical treatment is often performed at regional centers with advice from the staff at our facilities. As a result, the surgeons and pathologists at the regional centers do not have sufficient experience in the treatment of this disorder.

Because only 10–20 cases of diazoxide-unresponsive severe CHI are expected to arise in Japan each year,[20] one or two facilities dedicated to CHI would be sufficient to care for all patients with CHI in Japan and possibly in the entire region of East Asia. Domestic and international collaboration is necessary for better outcomes of patients with this disorder.

Future perspectives

There are several unanswered questions and unmet needs in regards to CHI that should be addressed in the near future. Some of the answers to these questions are on the horizon but are incomplete. Finding the answers to these questions is the responsibility of the current and future investigators in this field.

Questions

1 What are the genetic causes of the remaining 50% of cases of persistent CHI?
2 What are the causes of transient CHI?
3 What are the causes of so-called "adult nesidioblastosis"?
4 What would be the safe threshold of blood glucose to avoid neurological sequelae?
5 What is the mechanism of spontaneous remission of CHI?
6 How can we explain the dominance of paternal mutation in patients with diffuse CHI on 18F-DOPA PET?
7 Which type of CHI evolves into diabetes later in life?
8 Which novel diagnostic imaging modality is superior to 18F-DOPA PET?
9 How can we surgically manage diffuse, diazoxide-unresponsive CHI?
10 What novel medications could be used for diazoxide-unresponsive CHI?
11 How we can establish international collaborations so that all infants born with CHI will equally benefit from the current standard of care?

Acknowledgments

This work was supported by a grant-in-aid for scientific research from the Ministry of Health, Labour, and Welfare of Japan (Research on Measures for Intractable Diseases 2012-070). None of the authors has anything to disclose.

References

1 Jaffe R, Hashida Y, Yunis EJ. Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy. *Lab. Invest.* 1980; **42**: 356–65.
2 Rahier J, Fält K, Müntefering H, Becker K, Gepts W, Falkmer S. The basic structural lesion of persistent neonatal hypoglycaemia with hyperinsulinism: deficiency of pancreatic D cells or hyperactivity of B cells? *Diabetologia* 1984; **26**: 282–9.
3 Sempoux C, Guiot Y, Jaubert F, Rahier J. Focal and diffuse forms of congenital hyperinsulinism: the keys for differential diagnosis. *Endocr. Pathol.* 2004; **15**: 241–6.
4 Palladino AA, Stanley CA. Nesidioblastosis no longer! It's all about genetics. *J. Clin. Endocrinol. Metab.* 2011; **96**: 617–19.
5 McElroy MK, Lowy AM, Weidner N. Case report: focal nesidioblastosis ("nesidioblastoma") in an adult. *Hum. Pathol.* 2010; **41**: 447–51.
6 Menni F, de Lonlay P, Sevin C *et al.* Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics* 2001; **107**: 476–9.
7 Meissner T, Wendel U, Burgard P, Schaetzle S, Mayatepek E. Long-term follow-up of 114 patients with congenital hyperinsulinism. *Eur. J. Endocrinol.* 2003; **149**: 43–51.
8 Steinkrauss L, Lipman TH, Hendell CD, Gerdes M, Thornton PS, Stanley CA. Effects of hypoglycemia on developmental outcome in children with congenital hyperinsulinism. *J. Pediatr. Nurs.* 2005; **20**: 109–18.
9 Ludwig A, Ziegenhorn K, Empting S *et al.* Diabetes Patienten-Verlaufsdokumentationssystem (DPV) Group. Glucose metabolism and neurological outcome in congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; **20**: 45–9.
10 Shilyansky J, Fisher S, Cutz E, Perlman K, Filler RM. Is 95% pancreatectomy the procedure of choice for treatment of persistent hyperinsulinemic hypoglycemia of the neonate? *J. Pediatr. Surg.* 1997; **32**: 342–6.
11 Beltrand J, Caquard M, Arnoux JB *et al.* Glucose metabolism in 105 children and adolescents after pancreatectomy for congenital hyperinsulinism. *Diabetes Care* 2012; **35**: 198–203.
12 Leturque A, Brot-Laroche E, Le Gall M. GLUT2 mutations, translocation, and receptor function in diet sugar managing. *Am. J. Physiol. Endocrinol. Metab.* 2009; **296**: E985–92.
13 Matschinsky FM. Glucokinase as glucose sensor and metabolic signal generator in pancreatic beta-cells and hepatocytes. *Diabetes* 1990; **39**: 647–52.
14 Ashcroft FM, Rorsman P. K(ATP) channels and islet hormone secretion: new insights and controversies. *Nat. Rev. Endocrinol.* 2013; **9**: 660–9.
15 Olson TM, Terzic A. Human K(ATP) channelopathies: diseases of metabolic homeostasis. *Pflugers Arch.* 2010; **460**: 295–306.
16 Tesfaye N, Seaquist ER. Neuroendocrine responses to hypoglycemia. *Ann. N. Y. Acad. Sci.* 2010; **1212**: 12–28.
17 Achoki R, Opiyo N, English M. Mini-review: management of hypoglycaemia in children aged 0–59 months. *J. Trop. Pediatr.* 2010; **56**: 227–34.
18 De Leon DD, Stanley CA. Determination of insulin for the diagnosis of hyperinsulinemic hypoglycemia. *Best Pract. Res. Clin. Endocrinol. Metab.* 2013; **27**: 763–9.
19 Bruining G. Recent advances in hyperinsulinism and the pathogenesis of diabetes mellitus. *Curr. Opin. Pediatr.* 1990; **2**: 758–65.

20 Kawakita R, Sugimine H, Nagai S, Kawai M, Kusuda S, Yorifuji T. Clinical characteristics of congenital hyperinsulinemic hypoglycemia in infant: a nationwide epidemiological survey in Japan. *Nihon Shonika Gakkai Zasshi* 2011; **115**: 563–9 (in Japanese).
21 Mathew PM, Young JM, Abu-Osba YK *et al.* Persistent neonatal hyperinsulinism. *Clin. Pediatr. (Phila.)* 1988; **27**: 148–51.
22 Pearson ER, Boj SF, Steele AM *et al.* Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med.* 2007; **4**: e118.
23 Kapoor RR, Locke J, Colclough K *et al.* Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. *Diabetes* 2008; **57**: 1659–63.
24 Flanagan SE, Kapoor RR, Mali G *et al.* Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. *Eur. J. Endocrinol.* 2010; **162**: 987–92.
25 McGlacken-Byrne SM, Hawkes CP, Flanagan SE, Ellard S, McDonnell CM, Murphy NP. The evolving course of HNF4A hyperinsulinaemic hypoglycaemia–a case series. *Diabet. Med.* 2014; **31**: e1–5.
26 Stanescu DE, Hughes N, Kaplan B, Stanley CA, De Leon DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. *J. Clin. Endocrinol. Metab.* 2012; **97**: E2026–30.
27 Qi L, van Dam RM, Asselbergs FW, Hu FB. Gene-gene interactions between HNF4A and KCNJ11 in predicting type 2 diabetes in women. *Diabet. Med.* 2007; **24**: 1187–91.
28 Snider KE, Becker S, Boyajian L *et al.* Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 2013; **98**: E355–63.
29 Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *Eur. J. Endocrinol.* 2013; **168**: 557–64.
30 Thomas PM, Cote GJ, Wohllk N *et al.* Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy. *Science* 1995; **268**: 426–9.
31 Kane C, Shepherd RM, Squires PE *et al.* Loss of functional KATP channels in pancreatic beta-cells causes persistent hyperinsulinemic hypoglycemia of infancy. *Nat. Med.* 1996; **2**: 1344–7.
32 Dunne MJ, Kane C, Shepherd RM *et al.* Familial persistent hyperinsulinemic hypoglycemia of infancy and mutations in the sulfonylurea receptor. *N. Engl. J. Med.* 1997; **336**: 703–6.
33 Nestorowicz A, Inagaki N, Gonoi T *et al.* A nonsense mutation in the inward rectifier potassium channel gene, Kir6.2, is associated with familial hyperinsulinism. *Diabetes* 1997; **46**: 1743–8.
34 Huopio H, Reimann F, Ashfield R *et al.* Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. *J. Clin. Invest.* 2000; **106**: 897–906.
35 Thornton PS, MacMullen C, Ganguly A *et al.* Clinical and molecular characterization of a dominant form of congenital hyperinsulinism caused by a mutation in the high-affinity sulfonylurea receptor. *Diabetes* 2003; **52**: 2403–10.
36 Pinney SE, MacMullen C, Becker S *et al.* Clinical characteristics and biochemical mechanisms of congenital hyperinsulinism associated with dominant KATP channel mutations. *J. Clin. Invest.* 2008; **118**: 2877–86.
37 Ocal G, Flanagan SE, Hacihamdioglu B *et al.* Clinical characteristics of recessive and dominant congenital hyperinsulinism due to mutation(s) in the ABCC8/KCNJ11 genes encoding the ATP-sensitive potassium channel in the pancreatic beta cell. *J. Pediatr. Endocrinol. Metab.* 2011; **24**: 1019–23.
38 Rahier J, Sempoux C, Fournet JC *et al.* Partial or near-total pancreatectomy for persistent neonatal hyperinsulinaemic hypoglycaemia: the pathologist's role. *Histopathology* 1998; **32**: 15–19.
39 Suchi M, MacMullen C, Thornton PS, Ganguly A, Stanley CA, Ruchelli ED. Histopathology of congenital hyperinsulinism: retrospective study with genotype correlations. *Pediatr. Dev. Pathol.* 2003; **6**: 322–33.
40 Suchi M, Thornton PS, Adzick NS *et al.* Congenital hyperinsulinism: intraoperative biopsy interpretation can direct the extent of pancreatectomy. *Am. J. Surg. Pathol.* 2004; **28**: 1326–35.
41 Suchi M, MacMullen CM, Thornton PS *et al.* Molecular and immunohistochemical analyses of the focal form of congenital hyperinsulinism. *Mod. Pathol.* 2006; **19**: 122–9.
42 Rahier J, Guiot Y, Sempoux C. Morphologic analysis of focal and diffuse forms of congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; **20**: 3–12.
43 Bitner-Glindzicz M, Lindley KJ, Rutland P *et al.* A recessive contiguous gene deletion causing infantile hyperinsulinism, enteropathy and deafness identifies the Usher type 1C gene. *Nat. Genet.* 2000; **26**: 56–60.
44 Al Mutair AN, Brusgaard K, Bin-Abbas B *et al.* Heterogeneity in phenotype of usher-congenital hyperinsulinism syndrome: hearing loss, retinitis pigmentosa, and hyperinsulinemic hypoglycemia ranging from severe to mild with conversion to diabetes. *Diabetes Care* 2013; **36**: 557–61.
45 de Lonlay P, Fournet JC, Rahier J *et al.* Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy. *J. Clin. Invest.* 1997; **100**: 802–7.
46 Verkarre V, Fournet JC, de Lonlay P *et al.* Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia. *J. Clin. Invest.* 1998; **102**: 1286–91.
47 Capito C, de Lonlay P, Verkarre V *et al.* The surgical management of atypical forms of congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; **20**: 54–5.
48 Otonkoski T, Näntö-Salonen K, Seppänen M *et al.* Noninvasive diagnosis of focal hyperinsulinism of infancy with [18F]-DOPA positron emission tomography. *Diabetes* 2006; **55**: 13–18.
49 Hardy OT, Hernandez-Pampaloni M, Saffer JR *et al.* Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. *J. Clin. Endocrinol. Metab.* 2007; **92**: 4706–11.
50 Ribeiro MJ, Boddaert N, Delzescaux T *et al.* Functional imaging of the pancreas: the role of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy. *Endocr. Dev.* 2007; **12**: 55–66.
51 de Lonlay P, Simon-Carre A, Ribeiro MJ *et al.* Congenital hyperinsulinism: pancreatic [18F]fluoro-L-dihydroxyphenylalanine (DOPA) positron emission tomography and immunohistochemistry study of DOPA decarboxylase and insulin secretion. *J. Clin. Endocrinol. Metab.* 2006; **91**: 933–40.
52 Laje P, States LJ, Zhuang H *et al.* Accuracy of PET/CT scan in the diagnosis of the focal form of congenital hyperinsulinism. *J. Pediatr. Surg.* 2013; **48**: 388–93.
53 Yang J, Hao R, Zhu X. Diagnostic role of 18F-dihydroxyphenylalanine positron emission tomography in patients with congenital hyperinsulinism: a meta-analysis. *Nucl. Med. Commun.* 2013; **34**: 347–53.
54 Stanley CA, Lieu YK, Hsu BY *et al.* Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N. Engl. J. Med.* 1998; **338**: 1352–7.
55 Heslegrave AJ, Hussain K. Novel insights into fatty acid oxidation, amino acid metabolism, and insulin secretion from studying patients with loss of function mutations in 3-hydroxyacyl-CoA dehydrogenase. *J. Clin. Endocrinol. Metab.* 2013; **98**: 496–501.
56 Molven A, Matre GE, Duran M *et al.* Familial hyperinsulinemic hypoglycemia caused by a defect in the SCHAD enzyme

of mitochondrial fatty acid oxidation. *Diabetes* 2004; **53**: 221–7.
57 Flanagan SE, Patch AM, Locke JM *et al.* Genome-wide homozygosity analysis reveals HADH mutations as a common cause of diazoxide-responsive hyperinsulinemic-hypoglycemia in consanguineous pedigrees. *J. Clin. Endocrinol. Metab.* 2011; **96**: E498–502.
58 Glaser B, Kesavan P, Heyman M *et al.* Familial hyperinsulinism caused by an activating glucokinase mutation. *N. Engl. J. Med.* 1998; **338**: 226–30.
59 Christesen HB, Jacobsen BB, Odili S *et al.* The second activating glucokinase mutation (A456V): implications for glucose homeostasis and diabetes therapy. *Diabetes* 2002; **51**: 1240–6.
60 Cuesta-Muñoz AL, Huopio H, Otonkoski T *et al.* Severe persistent hyperinsulinemic hypoglycemia due to a de novo glucokinase mutation. *Diabetes* 2004; **53**: 2164–8.
61 Christesen HB, Brusgaard K, Beck Nielsen H, Brock Jacobsen B. Non-insulinoma persistent hyperinsulinaemic hypoglycaemia caused by an activating glucokinase mutation: hypoglycaemia unawareness and attacks. *Clin. Endocrinol. (Oxf.)* 2008; **68**: 747–55.
62 Christesen HB, Tribble ND, Molven A *et al.* Activating glucokinase (GCK) mutations as a cause of medically responsive congenital hyperinsulinism: prevalence in children and characterisation of a novel GCK mutation. *Eur. J. Endocrinol.* 2008; **159**: 27–34.
63 Osbak KK, Colclough K, Saint-Martin C *et al.* Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. *Hum. Mutat.* 2009; **30**: 1512–26.
64 Kassem S, Bhandari S, Rodríguez-Bada P *et al.* Large islets, beta-cell proliferation, and a glucokinase mutation. *N. Engl. J. Med.* 2010; **362**: 1348–50.
65 Hussain K. Mutations in pancreatic β-cell glucokinase as a cause of hyperinsulinaemic hypoglycaemia and neonatal diabetes mellitus. *Rev. Endocr. Metab. Disord.* 2010; **11**: 179–83.
66 Henquin JC, Sempoux C, Marchandise J *et al.* Congenital hyperinsulinism caused by hexokinase I expression or glucokinase-activating mutation in a subset of beta-cells. *Diabetes* 2013; **62**: 1689–96.
67 Gonzalez-Barroso MM, Giurgea I, Bouillaud F *et al.* Mutations in UCP2 in congenital hyperinsulinism reveal a role for regulation of insulin secretion. *PLoS One* 2008; **3**: e3850.
68 Otonkoski T, Kaminen N, Ustinov J *et al.* Physical exercise-induced hyperinsulinemic hypoglycemia is an autosomal-dominant trait characterized by abnormal pyruvate-induced insulin release. *Diabetes* 2003; **52**: 199–204.
69 Otonkoski T, Jiao H, Kaminen-Ahola N *et al.* Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells. *Am. J. Hum. Genet.* 2007; **81**: 467–74.
70 Arnoux JB, Verkarre V, Saint-Martin C *et al.* Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet. J. Rare. Dis.* 2011; **6**: 63.
71 Touati G, Poggi-Travert F, Ogier de Baulny H *et al.* Long-term treatment of persistent hyperinsulinaemic hypoglycaemia of infancy with diazoxide: a retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur. J. Pediatr.* 1998; **157**: 628–33.
72 Yoshida K, Kawai M, Marumo C *et al.* High prevalence of severe circulatory complications with diazoxide in premature infants. *Neonatology.* 2014; **105**: 166–71.
73 Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J. Pediatr.* 1993; **123**: 637–43.
74 Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J. Pediatr.* 1993; **123**: 644–50.
75 Yorifuji T, Kawakita R, Hosokawa Y *et al.* Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of KATP-channel hyperinsulinism. *Clin. Endocrinol. (Oxf.)* 2013; **78**: 891–7.
76 Laje P, Halaby L, Adzick NS, Stanley CA. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. *Pediatr. Diabetes* 2010; **11**: 142–7.
77 Ben-Ari J, Greenberg M, Nemet D, Edelstein E, Eliakim A. Octreotide-induced hepatitis in a child with persistent hyperinsulinemia hypoglycemia of infancy. *J. Pediatr. Endocrinol. Metab.* 2013; **26**: 179–82.
78 Koren I, Riskin A, Barthlen W, Gillis D. Hepatitis in an infant treated with octreotide for congenital hyperinsulinism. *J. Pediatr. Endocrinol. Metab.* 2013; **26**: 183–5.
79 Avatapalle B, Padidela R, Randell T, Banerjee I. Drug-induced hepatitis following use of octreotide for long-term treatment of congenital hyperinsulinism. *BMJ Case Rep.* 2012; doi: 10.1136/bcr-2012-006271.
80 Le Quan Sang KH, Arnoux JB, Mamoune A *et al.* Successful treatment of congenital hyperinsulinism with long-acting release octreotide. *Eur. J. Endocrinol.* 2012; **166**: 333–9.
81 Modan-Moses D, Koren I, Mazor-Aronovitch K, Pinhas-Hamiel O, Landau H. Treatment of congenital hyperinsulinism with lanreotide acetate (Somatuline Autogel). *J. Clin. Endocrinol. Metab.* 2011; **96**: 2312–17.
82 Kuhnen P, Marquard J, Ernert A *et al.* Long-term lanreotide treatment in six patients with congenital hyperinsulinism. *Horm. Res. Paediatr.* 2012; **78**: 106–12.
83 de Heide LJ, Laskewitz AJ, Apers JA. Treatment of severe postRYGB hyperinsulinemic hypoglycemia with pasireotide: a comparison with octreotide on insulin, glucagon, and GLP-1. *Surg. Obes. Relat. Dis.* 2013; doi: 10.1016/j.soard.2013.11.006.
84 Mohnike K, Blankenstein O, Pfuetzner A *et al.* Long-term non-surgical therapy of severe persistent congenital hyperinsulinism with glucagon. *Horm. Res.* 2008; **70**: 59–64.
85 Neylon OM, Moran MM, Pellicano A, Nightingale M, O'Connell MA. Successful subcutaneous glucagon use for persistent hypoglycaemia in congenital hyperinsulinism. *J. Pediatr. Endocrinol. Metab.* 2013; **26**: 1157–61.
86 von Rohden L, Mohnike K, Mau H *et al.* Visualization of the focus in congenital hyperinsulinism by intraoperative sonography. *Semin. Pediatr. Surg.* 2011; **20**: 28–31.
87 Laje P, Stanley CA, Palladino AA, Becker SA, Adzick NS. Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. *J. Pediatr. Surg.* 2012; **47**: 130–5.
88 Barthlen W, Mohnike W, Mohnike K. Techniques in pediatric surgery: congenital hyperinsulinism. *Horm. Res. Paediatr.* 2011; **75**: 304–10.
89 Barthlen W, de Lonlay P. Congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; **20**: 1–2.
90 Adzick NS, Thornton PS, Stanley CA, Kaye RD, Ruchelli E. A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. *J. Pediatr. Surg.* 2004; **39**: 270–5.
91 Barthlen W. Surgery in congenital hyperinsulinism – tips and tricks not only for surgeons. A practical guide. *Semin. Pediatr. Surg.* 2011; **20**: 56–9.
92 Glaser B, Ryan F, Donath M *et al.* Hyperinsulinism caused by paternal-specific inheritance of a recessive mutation in the sulfonylurea-receptor gene. *Diabetes* 1999; **48**: 1652–7.
93 de Lonlay-Debeney P, Poggi-Travert F, Fournet JC *et al.* Clinical features of 52 neonates with hyperinsulinism. *N. Engl. J. Med.* 1999; **340**: 1169–75.

94 Mohnike K, Wieland I, Barthlen W *et al.* Clinical and genetic evaluation of patients with K channel mutations from the German Registry for Congenital Hyperinsulinism. *Horm. Res. Paediatr.* 2014; **81**: 156–68.
95 Sogno Valin P, Proverbio MC, Diceglie C *et al.* Genetic analysis of Italian patients with congenital hyperinsulinism of infancy. *Horm. Res. Paediatr.* 2013; **79**: 236–42.
96 Su C, Gong C, Sanger P *et al.* Long-term follow-up and mutation analysis of 27 Chinese cases of congenital hyperinsulinism. *Horm. Res. Paediatr.* 2014; **81**: 169–176.
97 Yorifuji T, Kawakita R, Nagai S *et al.* Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism: predominance of paternally inherited monoallelic mutations in the KATP channel genes. *J. Clin. Endocrinol. Metab.* 2011; **96**: E141–5.
98 Bellanne-Chantelot C, Saint-Martin C, Ribeiro MJ *et al.* ABCC8 and KCNJ11 molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. *J. Med. Genet.* 2010; **47**: 752–9.
99 Banerjee I, Skae M, Flanagan SE *et al.* The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. *Eur. J. Endocrinol.* 2011; **164**: 733–40.
100 Masue M, Nishibori H, Fukuyama S *et al.* Diagnostic accuracy of [^{18}F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan. *Clin. Endocrinol. (Oxf.)* 2011; **75**: 342–6.

日本小児科学会雑誌　118巻9号　1342～1349（2014年）

原　著

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

木沢記念病院小児科[1]，同　放射線科[2]，大阪市立総合医療センター小児代謝・内分泌内科[3]
増江　道哉[1]　西堀　弘記[2]　高田　勲矢[1]　依藤　亨[3]

要　旨

先天性高インスリン血症の膵臓病変局在診断に18F-fluoro-L-DOPA positron emission tomography（18F-DOPA PET）検査は最も簡便で有用と考えられている．今回我々はK_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の31症例に18F-DOPA PET検査を実施した．遺伝子局在型のPET検査で局在型は61%，局在型の71%は頭部型であった．遺伝子診断は局在部位の同定はできないが，局在型かびまん型かの型判定に誤りはなく，PET検査の適応のスクリーニングとして有用であった．PET検査で同定された局在は病変とすべて一致した．しかし，病変の広がりまでは反映しない場合があった．選択的膵流入動脈カルシウム注入法はPET結果が遺伝子診断と一致しない場合やPETで病変が検出不能の場合に有用だが，侵襲的検査のため相補的に用いるのが良いと考えられた．日本人の先天性高インスリン血症は比較的軽症型が多く遺伝子局在型では2～6歳頃に自然治癒する傾向にあり神経学的後遺症も両側後頭葉白質萎縮とてんかんの2例のみであった．内科的治療による合併症・後遺症も少ないため，PETびまん型や手術の難しいPET頭部型は内科的治療を継続して自然治癒を待つのがよい選択であると考えられた．

キーワード：先天性高インスリン血症，K_{ATP}チャネル遺伝子異常，
18F-fluoro-L-DOPA positron emission tomography（18F-DOPA PET），
選択的膵流入動脈カルシウム注入法（arterial stimulation and venous sampling），
オクトレオチド

はじめに

先天性高インスリン血症は新生児・乳児期の持続性低血糖症の最も多い原因で，迅速・適切な治療をしないと，重篤な神経学的後遺症をきたす可能性がある．わが国における発症頻度は，出生3.5万人に1人であるとされている[1]．内科的治療に抵抗性のある先天性高インスリン血症は神経学的後遺症を回避するために外科的治療の適応となる．本症の膵臓病変はインスリノーマと異なり，CT・MRI・血管造影など一般の画像診断で病変の局在を同定することが困難であり，従来は盲目的に膵亜全摘が行われてきた．しかしながら，その結果は必ずしも満足できるものではなく，多くの症例で術後も低血糖が残存する一方，低血糖がコントロールされた症例の多くに術後糖尿病が発症した．18F-fluoro-L-DOPA（18F-DOPA）は膵β細胞に豊富に存在するDOPAデカルボキシラーゼによりβ細胞内に取り込まれるので，膵病変の局在は18F-DOPAを用いたpositron emission tomography（PET）検査により同定することが可能であると考えられている[2][3]．欧米では18F-DOPA PET検査により膵病変の局在を同定し，局所切除で後遺症なく治癒したとの報告が多くなされている[3]～[5]．国内では木沢記念病院が唯一の18F-DOPA PET検査施設であるため，全国の症例を検査解析してきた[6][7]．18F-DOPA PET検査は有用な検査であるが，感度や特異度において限界があるといわれている[4][5]．そこで今回我々は，木沢記念病院で18F-DOPA PET検査を実施した31症例を解析し，局在型診断のための他の検査との比較，内科的・外科的治療予後，合併症，神経学的後遺症を検討した．

（平成26年2月28日受付）（平成26年6月19日受理）
別刷請求先：（〒505-8503）美濃加茂市古井町下古井590
木沢記念病院小児科　増江　道哉
E-mail: masue@kizawa-memorial-hospital.jp

対象と方法

K_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の31症例（両親由来遺伝子異常3例，父親由来遺伝子異常28例；男児18例，女児13例；PET検査時年齢1か月～19歳）を対象として，2005年7月より2013年3月までに木沢記念病院で18F-DOPA PET検査を実施した．18F-DOPA PET検査の依頼元・症例治療中の施設一覧を表1に示す．

我々が，過去に報告したように[6]～[8]，局在型の診断方法には，1）遺伝子診断でK_{ATP}チャネル遺伝子異常が父由来の変異のヘテロ接合体である，2）画像診断として

表1 18F-DOPA PET検査の依頼元・症例治療中の施設一覧

国立成育医療センター 内分泌代謝科
神奈川県立こども医療センター 内分泌・代謝科
岐阜大学医学部附属病院 小児科
岐阜県立多治見病院 小児科
大垣市民病院 小児科
金沢医療センター 小児科
福井県済生会病院 小児科
福井県立病院 小児科
京都大学医学部附属病院 小児科
大阪市立総合医療センター 小児代謝・内分泌内科
大阪府立母子保健総合医療センター 消化器・内分泌科
西神戸医療センター 小児科
日本赤十字社和歌山医療センター 小児科
島根大学医学部附属病院 小児科
徳島大学病院 小児科
九州大学病院 小児科
九州厚生年金病院 小児科
佐賀大学医学部附属病院 小児科
佐賀病院 小児科
長崎市立市民病院 小児科
長崎大学病院 小児科
熊本大学医学部附属病院 小児科

北日本より順に記載

18F-DOPA PET検査で膵臓病変の局在を確認する，3) 選択的膵流入動脈カルシウム注入法（Arterial Stimulation and Venous Sampling，ASVS）で局在を確認する，4) 病理で局在を確認する（確定診断）の4つがある．18F-DOPA PET検査と他の診断検査の比較を行い，さらに2014年1月末時点までの臨床経過を通して内科的・外科的治療予後，合併症，神経学的後遺症について解析した．

本研究は，木沢記念病院の倫理委員会で承認されており，保護者の書面による承諾を得て行った．なお，現在は父由来K_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の症例のみを対象に，外来自由診療として一件20万円で実施している．

遺伝子検査[6)~8)]：患者，患者の父親，患者の母親の白血球ゲノムDNAを検体として，K_{ATP}チャネル遺伝子（*ABCC8*, *KCNJ11*）のエクソン，エクソン—イントロン境界領域，プロモーター領域の塩基配列をpolymerase chain reactionで増幅し直接塩基配列決定し解析した．遺伝子解析は，京都大学医学部附属病院（2009年以前）及び大阪市立総合医療センター（2010年以降）の倫理委員会承認の上，保護者の書面による承諾を得て行った．両親由来の遺伝子異常を認めた症例は遺伝子びまん型，父親由来の遺伝子異常のみを認めた症例は遺伝子局在型と判定した．

選択的膵流入動脈カルシウム注入法（Arterial Stimulation and Venous Sampling，ASVS）[7)8)]：薬物治療を2日間中止した上で輸液にて正常血糖を維持し，全身麻酔下で脾動脈・胃十二指腸動脈・上腸間膜動脈に順次カテーテルを入れてカルシウムを注入し，右肝静脈に挿入したカテーテルからインスリン・血糖値を測定した．インスリン値の2倍以上の上昇を有意（病変部位）と診断し，脾動脈有意はASVS膵体尾部型（体尾部の判別は不能），胃十二指腸動脈有意はASVS膵頭部型，上腸間膜動脈有意はASVS膵鉤部型と判定した．

18F-DOPA PET検査[6)~8)]：1) サイクロトロン（CYPRIS-HM18）を使用し18F-DOPAを合成した．2) ジアゾキサイドとグルカゴンは中止し，オクトレオチドは継続したままブドウ糖輸液で血糖を正常に保ち，6時間の絶食とした後，抱水クロラールとチアミラールナトリウムで鎮静した．3) PET装置（ADVANCE NXi scanner）にて，トランスミッション3分間実施後，18F-DOPA（5MBq/kg）を静注し，直後から60分後までダイナミック撮影した．4)PET検査後，直ちにCT撮影し，PET-CT合成画像を作成し，膵臓病変の局在を同定した（PET局在型，PETびまん型）．

結果（表2）

両親由来のK_{ATP}遺伝子異常（遺伝子びまん型）の3症例（症例1～3；*ABCC8*：3例）は，全てPETびまん型であった（図1a）．父由来のK_{ATP}遺伝子異常（遺伝子局在型）の28症例（症例4～31；*ABCC8*：24例，*KCNJ11*：4例）においては，PET局在型が17症例（61%：頭部＋鉤部12例，体部2例，尾部1例，頭体部1例，体尾部1例），PETびまん型が10症例（36%），感度以下でPET集積なしが1症例（3%）であった．

病理により診断が確定した症例のうちPET，ASVSをそれぞれ施行した5症例において，症例7はPET・ASVS・病理の結果が一致した．しかし，症例3ではびまん病変をPETびまん型・ASVS頭部型と診断し，症例14では体部病変をPET体部型・ASVS体尾部型と診断した．一方，症例5では体尾部病変をPETびまん型・ASVS体尾部型と診断し，症例16では頭部病変をPET検出不能・ASVS頭部型と診断した．

病理が確認された症例のうち遺伝子診断，PETが行われたのは16症例，うち遺伝子びまん型が3例，遺伝子局在型が13例であった．遺伝子びまん型の3例（症例1～3）はPETびまん型を示し，病理も一致した．遺伝子局在型13例（症例4～16）のうち10例（症例6～15）はPET局在型を示した．PET局在型10例中7例は局在集積を認めた部位と病変部位は一致したが，症例8で鉤部病変をPET頭部型と過大評価して診断（図2），症例13で頭体部病変をPET頭部型と過小評

表2　K_{ATP}チャネル遺伝子異常のある先天性高インスリン血症の31症例

No.	由来/K_{ATP}	性	現年齢	PET診断	ASVS診断	病理診断	手術年齢	急性期治療	現在までの治療経過	合併症	神経学的後遺症
	手術あり症例							(術前治療)			
1	両/ABCC8	男	3y8m	びまん		びまん	4m	オクト25μ	亜全摘：オクト継続→オクトLAR15mg/月		
2	両/ABCC8	女	6y1m	びまん		びまん	5m	ジアゾ・オクト15μ	亜全摘：インスリン投与開始継続中	胆石 糖尿病	後頭葉白質萎縮
3	両/ABCC8	女	8y4m	びまん	頭部	びまん	切除なし	オクト11μ	切除せず：オクト継続→オクトLAR 6mg/月		
4	父/ABCC8	女	5y11m	びまん		巨大局在	4m	グルカ・オクト18μ	亜全摘：インスリン投与開始継続中	胆石 糖尿病	
5	父/ABCC8	男	7y5m	びまん	体尾部	体尾部	1y7m	輸液・ジアゾ	体尾部切除：コーンスターチ→治癒（4y1m）		
6	父/ABCC8	男	1y2m	体尾部		体尾部	11m	オクト15μ	体尾部切除：術後治癒		
7	父/ABCC8	女	8y2m	鉤部	鉤部	鉤部	1y6m	オクト11μ	鉤部切除：術後治癒		
8	父/ABCC8	女	5y10m	頭部		鉤部	7m	ジアゾ・オクト10μ	鉤部切除：術後治癒		てんかん
9	父/ABCC8	女	1y6m	頭部		頭部	8m	オクト20μ	頭部切除：術後治癒		
10	父/ABCC8	男	3y11m	頭部		頭部	3m	オクト30μ	頭部切除：術後治癒		
11	父/KCNJ11	男	5y1m	頭部		頭部	3m	輸液	頭部切除：術後治癒		
12	父/ABCC8	女	2y3m	頭部		頭部	4m	輸液・オクト24μ	頭部切除（取り残し）：オクト継続→オクト5.9μ		
13	父/ABCC8	男	1y11m	頭部		頭体部	6m	輸液・オクト40μ	頭体部切除（Roux-en-Y再建）：術後治癒		
14	父/ABCC8	男	5y1m	体部	体尾部	体部	3m	オクト23μ	体部切除：術後治癒		
15	父/ABCC8	女	8y11m	体部		体尾部	6m	輸液	体尾部切除：術後治癒→5歳よりボグリボース	耐糖能異常	
16	父/ABCC8	男	4y9m	検出なし	頭部	頭部	9m	輸液・ジアゾ	頭部切除：術後治癒		
	手術なし症例							(最大治療)			
17	父/ABCC8	男	1y4m	びまん				オクト25μ	→オクト1.6μ	胆石	
18	父/ABCC8	男	2y6m	びまん				オクト6.3μ	→オクト5.5μ		
19	父/KCNJ11	女	3y10m	びまん				オクト23μ	→治癒（3y4m）		
20	父/ABCC8	男	6y6m	びまん				オクト14μ	→治癒（3y3m）		
21	父/ABCC8	女	6y10m	びまん				オクト2.3μ	→治癒（6y0m）		
22	父/ABCC8	男	7y6m	びまん				ジアゾ	→治癒（4y1m）		
23	父/ABCC8	女	9y0m	びまん				ジアゾ・オクト3.2μ	→治癒（5y11m）		
24	父/ABCC8	男	20y1m	びまん				ジアゾ	→治癒（4y）→17歳よりボグリボース	耐糖能異常	
25	父/KCNJ11	男	1y6m	頭体部				オクト25μ	→オクト3.4μ		
26	父/ABCC8	女	2y2m	頭部				オクト4.8μ	→オクト1.8μ		
27	父/ABCC8	男	2y7m	頭部				ジアゾ	→治癒（2y2m）		
28	父/ABCC8	男	2y7m	頭部				オクト8.5μ	→治癒（1y6m）		
29	父/ABCC8	男	3y2m	頭部				オクト15μ	→オクトLAR 15mg/月		
30	父/KCNJ11	女	3y11m	頭部				オクト5.8μ	→オクト3μ		
31	父/ABCC8	男	5y11m	尾部				ジアゾ	→治癒（1y10m）		

両：両親由来の遺伝子異常　父：父親由来の遺伝子異常　y：年齢　m：月齢　μ：μg/kg/日　オクト：オクトレオチド
ジアゾ：ジアゾキサイド　グルカ：グルカゴン
→の右は現在の状態を示す．治癒は内科的治療中止で（　）内は治癒年齢を示す．

価して診断（図3），症例15で体尾部病変をPET体部型と過小評価して診断（図4）していた．遺伝子局在型でPETびまん型の2症例中，症例4（図1b）は頭部から尾部までの巨大局在病変でありPET診断は正しかったが組織学的に正常なβ細胞も認められ，症例5（図1c）は体尾部病変でPETの頭部集積は偽陽性であった．遺伝子局在型でPET検出不能の症例16は病理では頭部病変であった．

手術を行ったPETびまん型5例（症例1～5）中実際に切除したのは4例で，そのうち2例（症例2, 4）は過剰切除でインスリン依存性糖尿病になり，1例（症例1）は病変部の残存で高インスリン血症の内科的治療を

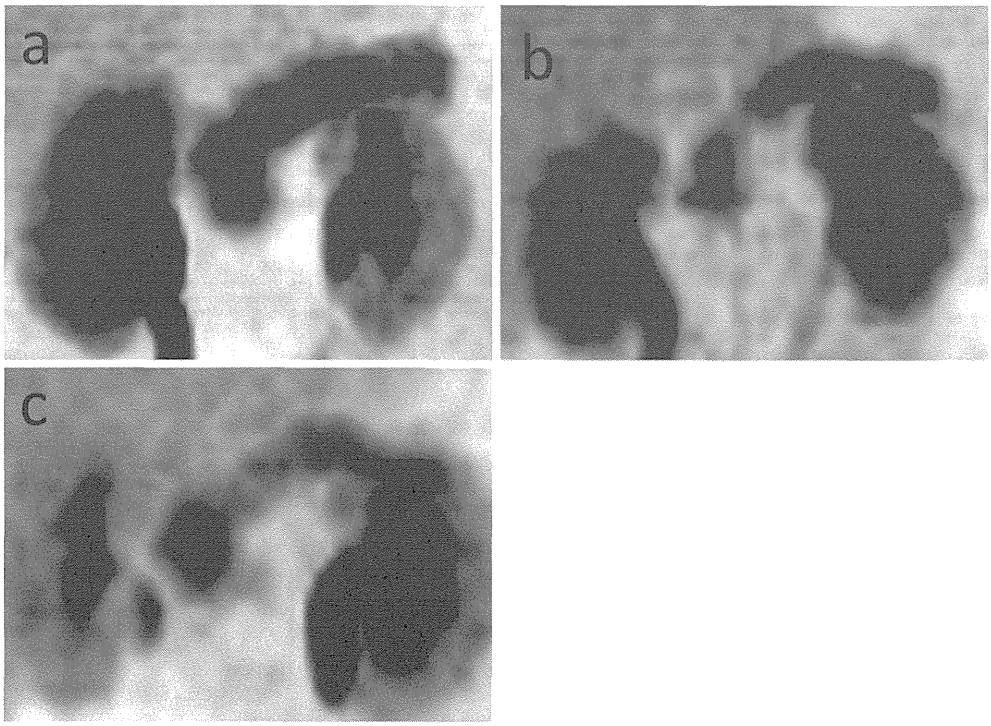

図1　PET びまん型の 18F-DOPA PET 画像
a（症例 3）：遺伝子びまん型，病理びまん病変；b（症例 4）：遺伝子局在型，病理巨大局在病変；c（症例 5）：遺伝子局在型，病理体尾部病変（PET の頭部集積は偽陽性）

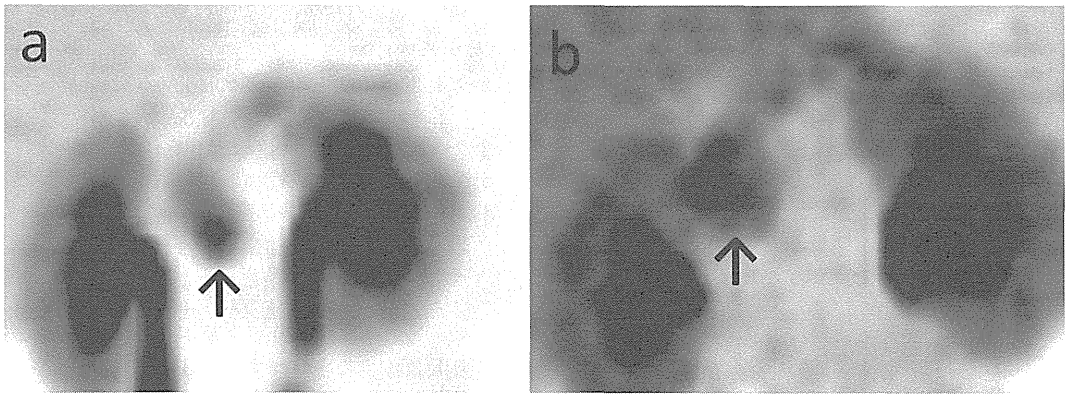

図2　病理膵鉤部病変の 18F-DOPA PET 画像
a（症例 7）：遺伝子局在型，PET 膵鉤部型；b（症例 8）：遺伝子局在型，PET 膵頭部型（PET の鉤部以外の頭部集積は偽陽性）．↑は集積部位を示す．

継続し，1 例（症例 5）は食事療法を継続した後 4 歳で治癒した．手術を行った PET 局在型 10 例（症例 6～15）中 9 例（90%）は内科的治療を中止できたが，症例 12（頭部病変）は病変が完全に摘出できず術後も内科的治療を必要とした．PET で検出出来なかった症例 16（頭部病変）は術後治癒した．

手術を実施しなかった 15 症例（症例 17～31）は，内科的治療継続中に治癒ないしは軽快傾向を認めた．PET びまん型 8 例（症例 17～24）中 2 例（症例 17, 18）はオクトレオチド減量中で，6 例（症例 19～24）は平均 4 歳 5 か月（3 歳 3 か月～6 歳）で治癒した．PET 局在型 7 例（症例 25～31）中 4 例（症例 25, 26, 29, 30）はオクトレオチド減量中で，3 例（症例 27, 28, 31）は平均 1 歳 10 か月（1 歳 6 か月～2 歳 2 か月）で治癒した．

合併症は，オクトレオチドによる胆石を 3 例（症例 2, 4, 17）に認めた．PET びまん型で膵亜全摘した 3 症例（症例 1, 2, 4）では，症例 1 が病変部の残存により内科的治療の継続を要し，症例 2, 4 がインスリン依存性糖尿病となった．また，PET 局在型で膵部分切除の症例 15 と PET びまん型で内科的治療継続の症例 24

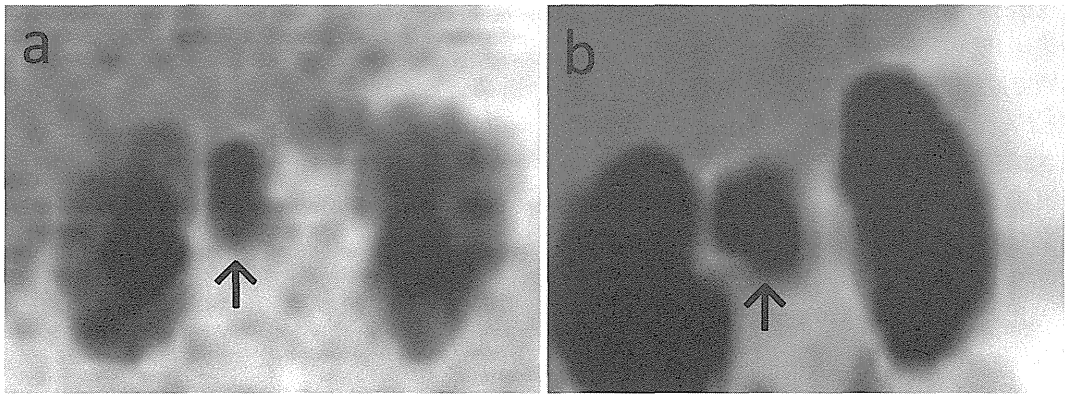

図3　PET 膵頭部型の 18F-DOPA PET 画像
a（症例 12）：遺伝子局在型，病理頭部病変；b（症例 13）：遺伝子局在型，病理頭体部病変（PET の膵体部は偽陰性）．↑は集積部位を示す．

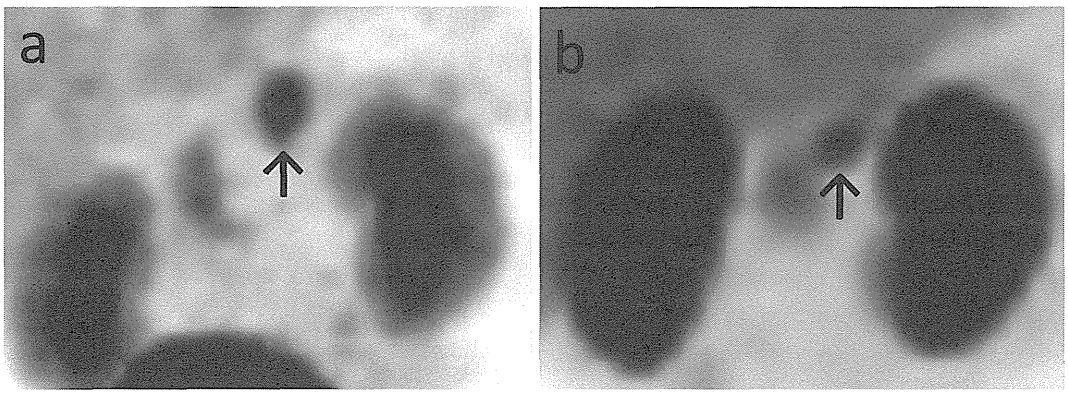

図4　PET 膵体部型の 18F-DOPA PET 画像
a（症例 14）：遺伝子局在型，病理体部病変；b（症例 15）：遺伝子局在型，病理体尾部病変（PET の膵尾部は偽陰性）．↑は集積部位を示す．

で耐糖能異常を認めα-グルコシダーゼ阻害薬（ボグリボース）投与を必要とした．

神経学的後遺症は，症例2の両側後頭葉白質萎縮と症例8のてんかんの2例であった．

考　察

今回我々の実施した遺伝子局在型の PET 検査で，PET びまん型が 10 例（36%），PET 局在型が 17 例（61%）であった．遺伝子局在型がびまん病変や PET びまん型であった症例は文献的にも報告されている．Banerjee らは遺伝子局在型の 13 例中 4 例（31%）がびまん病変で膵亜全摘が必要であったと報告した[9]．Bellanné-Chantelot らの報告では[10]，遺伝子局在型の 35 例において，手術症例 25 例中 3 例（12%）がびまん病変で，手術していない症例 10 例中 8 例（80%）が PET か ASVS でびまん型で，合計すると遺伝子局在型 35 例中 11 例（31%）が病理・PET・ASVS のいずれかでびまん型と診断されていた．Bellanné-Chantelot らは，遺伝子局在型がびまん病変になる機序については説明できないと述べている[10]．我々の遺伝子局在型で PET びまん型の2症例（症例 4, 5）の病理を検討した限りでは，PET びまん型は大きな局在病変で境界不明瞭な散在性病変であったため，PET で正確な病変部位を同定しにくかった可能性がある．症例5は PET びまん型であったが病理の結果は境界不明瞭な散在性体尾部病変であった．しかし，1歳7か月に体尾部切除したにもかかわらず術後コーンスターチ療法を継続し，完全に治癒したのは4歳1か月であり，膵頭部にも病変が残っていた可能性も考えられた．

今回の症例において PET 局在型の 17 例中 12 例（71%）は頭部型であった．膵頭部の局在頻度が高い理由は体尾部に比べて頭部の膵臓全体に占める体積が大きいためと考えられた．

18F-DOPA PET 検査以外の局在型の診断方法には，遺伝子診断・ASVS・病理診断（確定診断）がある．過去の論文でも述べられているように[10]，今回の症例に

おいても遺伝子びまん型は，全て病理でもびまん病変であり今後はPET検査の対象外と考えられた．また，遺伝子診断で遺伝子局在型と判定された場合は，たとえPETびまん型であっても病理では正常β細胞の存在が確認され遺伝子診断による局在型かびまん型かの型判定に誤りはなかった．しかし，遺伝子診断で局在同定は出来ないため，遺伝子診断はPET検査の適応症例をスクリーニングするのに有用であった．PETとASVSの比較において，症例3ではびまん病変をPETびまん型・ASVS頭部型と診断し，症例14では体部病変をPET体部型・ASVS体尾部型(ASVSでは体部病変と尾部病変は区別出来ない）と診断し，PETのほうがASVSより有用であった．一方，症例5では体尾部病変をPETびまん型（頭部偽陽性）・ASVS体尾部型と診断し，症例16では頭部病変をPET検出不能・ASVS頭部型と診断し，ASVSのほうがPETより有用であった．ASVSは18F-DOPA PET検査と相補関係にあり，PET検査結果が遺伝子診断と相違する場合・PETで病変が検出出来ない場合に有用であったが誤診例もあった．ASVSは膵鉤部と膵頭部を識別できる可能性がある点でPET検査より優位であるが，膵体部と膵尾部の識別が出来ない・検査前に内科的治療を2日間中止する必要がある・手技が難しい・侵襲的検査であることよりPET検査の結果が遺伝子検査の結果と一致しない場合に実施する検査になると考えられた．

今回のPET検査において，PET検査で局在が同定された場合は全て該当部位に病変が認められた．しかし，病変部位を過小評価・過大評価して病変局在を示しても広がりを反映しない場合があり，症例5, 8で膵頭部の偽陽性，症例13, 15で膵体尾部の偽陰性が認められた．原因の一つとして膵頭部は膵体・尾部に比べて容積が大きいため，放射線学的に部分容積効果で集積が強くなりやすいことが考えられた．Ribeiroらは PETびまん型の解析で，膵頭部は膵体尾部に比べて8.7% 集積が強かったと報告しており[5]，集積の定量評価をするときに注意が必要である．また，Capitoらは PETでは病変の広がりでなくDOPAの取り込み活性の強い部位を捉えているため正確な病変部位の同定は出来ないと報告している[11]．

治療予後に関しては，遺伝子局在型ではPET局在型で平均1歳10か月(1歳6か月～2歳2か月)，PETびまん型で平均4歳5か月（3歳3か月～6歳）に自然治癒した．欧米の報告でも，遺伝子局在型で5歳，遺伝子びまん型で10歳頃には自然治癒することが多いといわれている[12]．しかし，欧米では先天性高インスリン血症に対して積極的に手術することが多く，フィラデルフィア小児病院では，オクトレオチド15μg/kg/日投与しても血糖コントロール出来ない症例は神経学的予後を考慮の上，病変の部位にかかわらず手術する方針とされている．日本人の先天性高インスリン血症は欧米人に比べて軽症型が多く，内科的治療による合併症・神経学的後遺症も少ないため，PETびまん型や手術の難しいPET頭部型は内科的治療を継続して自然治癒を待つのがよい選択であると考えられた[13][14]．

合併症は膵亜全摘後のインスリン依存性糖尿病を除けば，オクトレオチドによる胆石や耐糖能異常など軽度なものだけであった．

神経学的後遺症も治療が必要なものは症例8のてんかんのみで，カルバマゼピン内服中である．症例2はMRIで両側後頭葉白質萎縮を認めたが髄鞘化と発達は正常で視覚刺激に対する反応性も良好であった．しかし，因果関係不明なものも含めると，症例28は複雑型熱性けいれんを認めたが脳波と頭部MRIに異常は認められなかった．また，症例30は揺さぶられっ子症候群による硬膜下血腫で発達の遅れが認められているが，その他の症例はすべて発達の遅れを認めなかった．ただし，症例1は一時的に軽度の自閉症スペクトラムの疑いがあり，症例15は一時的に注意欠損/多動性障害の疑いがあったが，2014年1月末の調査時は正常と判定された．

最後に，先天性高インスリン血症の膵臓病変局在診断に18F-DOPA PET検査は簡便で有用な検査であるが，感度や特異度において限界がある．今後18F-DOPA PET検査の評価と精度向上のためには，臨床経過のフォローと病理による局在の確定診断と比較した評価が重要であり，さらに症例の蓄積が必要である．

結　論

18F-DOPA PET検査は，局在型の先天性高インスリン血症の病変部位診断には非侵襲的で極めて有用な検査で，局在性集積を認めた場合は病変を診断できる検査である．外科的治療を考慮する場合，本検査を施行することにより盲目的な膵亜全摘が回避でき，適切な部分切除が行えることで術後治癒率を向上させることができると考えられた．

しかし，非典型例においては，病変局在を示しても広がりを反映しない場合があり，膵頭部の偽陽性と膵体・尾部の偽陰性に注意が必要であると考えられた．

日本人の先天性高インスリン血症は欧米人に比べて自然治癒が期待される軽症型が多く，内科的治療による合併症・神経学的後遺症も少ないため，PETびまん型や手術の難しいPET頭部型は内科的治療を継続して自然治癒を待つのがよい選択であると考えられた．

謝辞　PET検査の18F-DOPA試薬の合成にご協力いただいた，社会医療法人厚生会木沢記念病院中部療護セン

ター福山誠介氏に深謝いたします．本研究の遺伝子解析，PET診断に関わる部分については厚生労働省難治性疾患克服研究事業（H21-難治-一般-189, H22-難治-一般-101, H24-難治-一般-070）の補助を受けました．

日本小児科学会の定める利益相反に関する開示事項はありません．

文　献

1) 川北理恵，杉峰啓憲，長井静世，他．本邦における先天性高インスリン血症の実態調査．日児誌 2011；115：563—569.
2) Otonkoski T, Veijola R, Huopio H, et al. Diagnosis of focal persistent hyperinsulinism of infancy with 18F-fluoro-L-DOPA PET (Abstract). Horm Res 2003；60：2.
3) Ribeiro MJ, De Lonlay P, Delzescaux T, et al. Characterization of hyperinsulinism in infancy assessed with PET and 18F-fluoro-L-DOPA. J Nucl Med 2005；46：560—566.
4) Hardy OT, Hernandez-Pampaloni M, Saffer JR, et al. Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. J Clin Endocrinol Metab 2007；92：4706—4711.
5) Ribeiro MJ, Boddaert N, Bellanné-Chantelot C, et al. The added value of [18F]fluoro-L-DOPA PET in the diagnosis of hyperinsulinism of infancy：a retrospective study involving 49 children. Eur J Nucl Med Mol Imaging 2007；34：2120—2128.
6) Yorifuji T, Kawakita R, Nagai S, et al. Molecular and clinical analysis of Japanese patients with persistent congenital hyperinsulinism：predominance of paternally inherited monoallelic mutations in the KATP channel genes. J Clin Endocrinol Metab 2011；96：E141—E145.
7) Masue M, Nishibori H, Fukuyama S, et al. Diagnostic accuracy of [18F]-fluoro-L-dihydroxyphenylalanine positron emission tomography scan for persistent congenital hyperinsulinism in Japan. Clin Endocrinol 2011；75：342—346.
8) 長井静世，依藤　亨，土井　拓，他．集学的アプローチにより腫瘍核出術をしえた局所型先天性高インスリン血症．日児誌　2009；113：838—842.
9) Banerjee I, Skae M, Flanagan SE, et al. The contribution of rapid KATP channel gene mutation analysis to the clinical management of children with congenital hyperinsulinism. Eur J Endocrinol 2011；164：733—740.
10) Bellanné-Chantelot C, Saint-Martin C, Ribeiro MJ, et al. *ABCC8* and *KCNJ11* molecular spectrum of 109 patients with diazoxide-unresponsive congenital hyperinsulinism. J Med Genet 2010；47：752—759.
11) Capito C, Khen-Dunlop N, Ribeiro MJ, et al. Value of 18F-fluoro-L-dopa PET in the preoperative localization of focal lesions in congenital hyperinsulinism. Radiology 2009；253：216—222.
12) Mazor-Aronovitch K, Landau H, Gillis D. Surgical versus non-surgical treatment of congenital hyperinsulinism. Pediatr Endocrinol Rev 2009；6：424—430.
13) 松原康策，和田珠希，依藤　亨，他．3年間のオクトレオチド持続皮下注射により膵手術を回避できた先天性高インスリン血症．日児誌　2011；115：1445—1450.
14) Yorifuji T, Kawakita R, Hosokawa Y, et al. Efficacy and safety of long-term, continuous subcutaneous octreotide infusion for patients with different subtypes of KATP-channel hyperinsulinism. Clin Endocrinol 2013；78：891—897.

Diagnostic Accuracy of 18F-DOPA PET to Localize K_{ATP}-channel Hyperinsulinism and Post-treatment Prognosis

Michiya Masue[1], Hironori Nishibori[2], Izaya Takada[1] and Tohru Yorifuji[3]
[1]Department of Pediatrics, Kizawa Memorial Hospital
[2]Department of Radiology, Kizawa Memorial Hospital
[3]Department of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital

To evaluate the accuracy of 18F-fluoro-L-DOPA positron emission tomography (18F-DOPA PET) for diagnosing and localizing K_{ATP}-channel focal congenital hyperinsulinism in Japan, we performed 18F-DOPA PET scanning on 31 patients. Three of our patients had biparental mutations and they all showed diffuse uptake while the remaining 28 patients had paternal mutations. Seventeen out of 28 paternal mutations (61%) showed focal uptake. Twelve of these 17 patients (71%) showed uptake in the head of the pancreas. We diagnosed the pancreatic lesion correctly when 18F-DOPA PET showed a small focal uptake. However, the actual lesion borders were occasionally smaller or larger than shown on PET images.

Genetic testing had a 0% misdiagnosis rate but was useless for determining the lesion's location. It was useful to screen for PET scanning. The arterial stimulation venous sampling test (ASVS) occasionally provided more useful results than the 18F-DOPA PET test. However, ASVS is an invasive test. It is most useful in cases where 18F-DOPA PET and genetic test results are inconsistent.

Out of these 31 patients, two developed insulin-dependent diabetes mellitus following near total pancreatectomy. One patient (3%) showed epilepsy, but the other 30 patients showed no obvious neurological complications.

Japanese patients with congenital hyperinsulinism typically have relatively mild symptoms. Most of the patients who receive pharmacological therapy show spontaneous remission at 2 to 6 years of age. Our study suggests that continuous medical treatments such as octreotide therapy until spontaneous resolution can be a useful alternative to surgery for patients with diffuse or head accumulation of 18F-DOPA PET, because surgery is highly complex and there is risk of lasting complications.