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.

b. 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]

1) Genetic causes of persistent CHI

(a) K_{ATP} channel CHI

The most commonly known genetic cause of persistent CHI is inactivating 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.[38-43] Basically, all β cells in the pancreas are abnormal in both recessive and dominantly inherited forms (diffuse lesion).

(b) 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.[44,45]

2) 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 section 6).

The focal form of CHI occurs in patients who have a paternally inherited monoallelic mutation in one of the K_{ATP} channel genes.[46,47] 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.[46,47] 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.[48] 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.

3) 18F-fluoro-L-DOPA positron emission tomography

Together with the molecular diagnosis of a paternally inherited mutation, the development of an imaging modality, 18F-fluoro-L-DOPA positron emission tomography (18F-DOPA PET), to localize the focal lesion has changed the management of patients with CHI.[49-54] 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 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.[49]

4) Other genetic causes of persistent CHI

(a) 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).[55] 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.

(b) 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.[56] Therefore, recessively inherited biallelic inactivating mutations in HADH lead to overactivity of GDH and hyperinsulinism.[56,57] 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.[58]

(c) 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.[59-66] 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.[62] Recently, a novel type of focal CHI presumably caused by a somatic mutation of glucokinase has been reported.[67]

(d) 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.[68]

(e) 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.[69,70] 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.

6. 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.

a. 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.[71] 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.[9,72] 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.[73]

b. Octreotide and other somatostatin analogues

1) 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.[74,75] 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.[76] 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[77] and hepatitis[78-80] 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 under way in Japan (UMIN Clinical Trials Registry, UMIN000012620, SCORCH study).

2) 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,[81] lanreotide,[82,83] and pasireotide.[84] 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.

c. 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.[85,86]

d. 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,[87] 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[88,89] but is a major operation and not without postoperative complications.[90] 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.[76,85]

7. Global and Japanese perspectives on CHI

a. Global trends in the management of CHI

1) 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.[91]

2) 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.[90,92] 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.

b. 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.

1) Different molecular background of CHI

Previous reports from Israel and France showed that approximately 40% of patients with surgically treated CHI had focal lesions.[93,94] 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.[95] Similar studies from other countries have reported different figures; in the United Kingdom,[29] Italy,[96] and China,[97] 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[98]; 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,[99,100] but it appears that identification of focal CHI is even more important for Japanese patients.

2) Different accuracy of 18F-DOPA PET

Previous reports have repeatedly shown the efficacy of 18F-DOPA PET in localizing focal CHI.[49-54] 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.[101] 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 white 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 white patients, most of these patients had greater uptake in terms of standardized uptake value compared with Japanese patients.

3) 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.[88,89] 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.[76] Many of these patients could later be weaned off treatment with spontaneous remission of the disease.

4) 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] 1 or 2 facilities dedicated to CHI is 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.

8. Future perspectives

There are several unanswered questions and unmet needs in regard 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).

Conflict of interest

None declared.

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: 617–9.

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 (in Japanese). *Nihon. Shonika Gakkai Zasshi.* 2011; 115: 563–9.

21. Mathew PM, Young JM, Abu-Osba YK, et al. Persistent neonatal hyperinsulinism. *Clin. Pediatr. (Phila).* 1988; 27: 148–151.

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. 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.

43. Rahier J, Guiot Y, Sempoux C. Morphologic analysis of focal and diffuse forms of congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; 20: 3–12.

44. 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.

45. 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.

46. 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.

47. 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.

48. 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.

49. 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: 13–8.

50. 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.

51. 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.

52. 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.

53. 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.

54. 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.

55. 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.

56. 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.

57. 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.

58. 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.

59. Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. *N. Engl. J. Med.* 1998; 338: 226–30.

60. 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.

61. 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.

62. 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: 1011.

63. 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.

64. 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.

65. 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.

66. Hussain K. Mutations in pancreatic ß-cell glucokinase as a cause of hyperinsulinaemic hypoglycaemia and neonatal diabetes mellitus. *Rev. Endocr. Metab. Disord.* 2010; 11: 179–83.

67. 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.

68. 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.

69. 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.

70. 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.

71. Arnoux JB, Verkarre V, Saint-Martin C, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy. *Orphanet. J. Rare. Dis.* 2011; 6: 63.

72. 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.

73. Yoshida K, Kawai M, Marumo C, et al. High prevalence of severe circulatory complications with diazoxide in premature infants. *Neonatology.* 2014; 105: 166–71.

74. 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.

75. Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J. Pediatr.* 1993; 123: 644–50.

76. 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.

77. 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.

78. 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.

79. 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.

80. 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; 2012.

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: 2312–7.

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. 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.

84. 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 Dec 4 [Epub ahead of print].

85. 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.

86. 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.

87. 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.

88. 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.

89. Barthlen W, Mohnike W, Mohnike K. Techniques in pediatric surgery: congenital hyperinsulinism. *Horm. Res. Paediatr.* 2011; 75: 304–10.

90. Barthlen W, de Lonlay P. Congenital hyperinsulinism. *Semin. Pediatr. Surg.* 2011; 20: 1–2.

91. 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.

92. Barthlen W. Surgery in congenital hyperinsulinism-tips and tricks not only for surgeons. A practical guide. *Semin. Pediatr. Surg.* 2011; 20: 56–9.

93. 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.

94. 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.

95. 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 Jan 7 [Epub ahead of print].

96. 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.

97. 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 Jan 9 [Epub ahead of print].

98. 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.

99. 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.

100. 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.

101. 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.

Legends for figures

Figure 1 Glucose-induced insulin secretion pathway. The 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.

Table 2. Known etiologies 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

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 beta-hydroxybutyrate level <2.0 mmol/L
Glucose infusion rate to maintain normoglycemia: >6–8 mg/kg/min

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)

	HNF1A	AD

AD, autosomal dominant; AR, autosomal recessive.