Surgery for Congenital Hyperinsulinism

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Abstract

Transient hypoglycemia in the newborn period is common and generally associated either with immaturity of the glucose regulatory pathways (which responds to frequent feeds and resolves spontaneously within hours), or with stress-associated hyperinsulinism (which responds well to hyperglycemic drugs and resolves spontaneously within the first few weeks or months of life). Congenital Hyperinsulinism (HI) is the most frequent cause of persistent, long-term hypoglycemia in newborns and infants, and can lead to severe and irreversible brain damage and developmental delay. It is a rare congenital disorder of the glucose metabolism that has an estimated incidence of 1–1.4 cases per 50,000 live births, leading to about 80–120 new cases in the United States each year. An incidence as high as 1 in 2500 live births has been reported in populations with high consanguinity like Arabians and Ashkenazi Jews. Inappropriate oversecretion of insulin is the hallmark of HI, and the genetic background is quite variable. Depending on the genetic mutation, babies with HI may be treated medically or may require surgery either as a palliative treatment or as a definitive cure.

Keywords

Congenital pancreatic disease • Congenital hyperinsulinism • Surgery

45.1 Introduction

Transient hypoglycemia in the newborn period is common and generally associated either with immaturity of the glucose regulatory pathways (which responds to frequent feeds and resolves spontaneously within hours), or with stress-associated hyperinsulinism (which responds well to hyperglycemic drugs and resolves spontaneously within the first few weeks or months of

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life). Congenital Hyperinsulinism (HI) is the most frequent cause of persistent, *long-term* hypoglycemia in newborns and infants, and can lead to severe and irreversible brain damage and developmental delay. It is a rare congenital disorder of the glucose metabolism that has an estimated incidence of 1–1.4 cases per 50,000 live births, leading to about 80–120 new cases in the United States each year [1, 2]. An incidence as high as 1 in 2500 live births has been reported in populations with high consanguinity like Arabians and Ashkenazi Jews. Inappropriate oversecretion of insulin is the hallmark of HI, and the genetic background is quite variable. Depending on the genetic mutation, babies with HI may be treated medically or may require surgery as either a palliative treatment or as a definitive cure.

45.2 History

Congenital hyperinsulinism was first described by McQuarrie in 1954, who initially termed it "syndrome of idiopathic hypoglycemia of infants" [3]. At that time, assays for the accurate measurement of plasma insulin were not available. However, he suggested that there could be an association between the disease and a state of hyperinsulinism, and he also highlighted the "high incidence of a familial or genetic trait of the disease". The first pancreatectomy performed on a child with HI was reported in 1934 by Evarts Graham, 20 years before the disease was described. The pancreas was explored searching for an adenoma, but since no evidence of an adenoma was found, a near-total pancreatectomy [~90%] was performed, and the patient's hypoglycemia resolved [4]. The revolutionary development of an insulin radioimmunoassay in the late 1950s by Nobel Prize laureate Rosalyn Yalow confirmed that insulin oversecretion was crucial to the pathophysiology of HI [5]. For decades it was believed that insulin was secreted by an excessive number of islets resulting from *nesidioblastosis*, an abnormal postnatal budding of endocrine cells off the pancreatic ducts ("nesidion" = island). This theory, proposed by Yakovac et al. at the Children's Hospital of Philadelphia (CHOP), came from the histologic analysis of pancreatic specimens from HI cases stained with insulin-specific techniques. Later studies in the 1980s showed that nesidioblastosis was in fact a normal neonatal phenomenon, and the term "nesidioblastosis" has been abandoned [6, 7]. Advances in molecular biology and genetics led to our current understanding of the disease, which occurs due to a variety of genetic derangements that alter the regulatory mechanisms of glucose homeostasis.

45.3 Pathophysiology

Glucose homeostasis is complex and is influenced by a large number of factors. Plasma glucose levels are maintained within the normal range by mechanisms that respond to the postprandial and fasting states in opposite directions. During the postprandial state, the liver accumulates glucose in the form of glycogen (glycogenogenesis), while during the fasting state, the liver releases glucose by glycogenolysis. Multiple hormones and factors promote glycogenolysis and hyperglycemia: glucocorticoids, glucagon, catecholamines, somatostatin and others. However, insulin is the only endogenous hormone that reduces plasma glucose levels. Insulin inhibits glucose release from the liver and promotes glucose uptake in peripheral tissues. When the plasma glucose level rises, glucose enters the beta cell's cytoplasm through the high-capacity GLUT-2 transporter, which is followed by an increase in intracellular glucose metabolism. As a consequence, the intracellular concentration of ATP increases (as does the ATP/ADP ratio), and the ATP-dependent potassium channels (K-ATP channel) located in the cytosolic membrane of the beta cell become inactive and close. Potassium accumulates on the inner surface of the cytoplasmic membrane and depolarizes it. The depolarization generates the activation of voltage-dependent calcium channels and calcium accumulates in the cytoplasm, which eventually triggers a calcium-dependent insulin exocytosis (Fig. 45.1). When the K-ATP channel located in the cytoplasmic membrane is defective due to *loss-of-function*

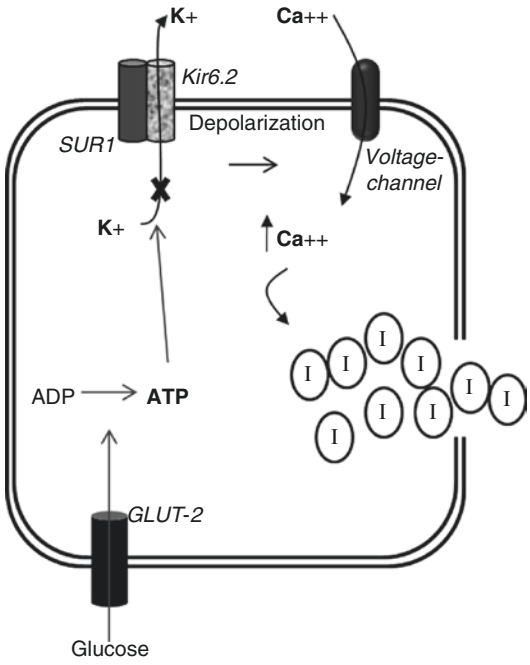

Fig. 45.1 Insulin release as a physiologic response to hyperglycemia. The ATP/ADP ratio increases as a consequence of the glucose metabolism. The ATP-sensitive potassium channel reacts to this by closing. The accumulation of potassium in the cytoplasmic surface of the beta-cell membrane depolarizes it. This event triggers an influx of calcium through voltage-sensitive calcium channels, which in turn generates a calcium-dependent insulin release. *SUR1* sulfonylurea receptor 1, *Kir6.2* inward-rectifier potassium ion channel 6.2, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *GLUT-2* glucose transporter 2, *I* insulin

genetic mutations, it remains inactivated at all times, regardless of the plasma glucose level, generating a non-regulated, persistent, insulin release that leads to unregulated hypoglycemia. This is the most common pathophysiologic mechanism of HI. The insulin levels, however, are never strikingly elevated in HI. The K-ATP channel is composed of 2 subunits: SUR1 (a sulfonylurea receptor, the regulatory subunit) and Kir6.2 (the ion pore), which are encoded by adjacent genes located in the short arm of chromosome 11. Less commonly, HI occurs due to genetic defects in other enzymes. Pancreatic glutamate dehydrogenase (GDH) is a mitochondrial enzyme that catalyzes the reversible oxidation of glutamate to alpha-ketoglutarate (and ammonia), which after a series of intermediate steps through the tricarboxylic acid cycle results in an elevation of the intracellular ATP/ADP ratio and consequently an insulin release. *Gain-of-function* mutations in the GDH gene lead to HI and hyperammonemia ("hyperinsulinism/hyperammonemia [HI/HA] syndrome") [8, 9]. Pancreatic glucokinase (GK) produces the phosphorylation of intracellular glucose to glucose-6-phosphate (G6-P), which is the first step of the glycolytic pathway that will ultimately increase the production of ATP and stimulate insulin release. GK has a low affinity for glucose and is not self-regulated by its end product G6-P. Gain-of-function mutations in the GK gene increase the affinity of GK for glucose so that more insulin is released at any given plasma glucose level, which in turn leads to HI (although most of these cases have a mild clinical course) [10, 11]. More recently, deficiencies in the mitochondrial fatty acid beta-oxidation enzyme "short-chain hydroxyacyl-CoA dehydrogenase" (SCHAD) have been identified as a rare cause of HI, and the mechanism appears to be a loss of the natural inhibitory effect that SCHAD exerts on the mitochondrial GDH [12].

45.4 Diagnosis

The diagnosis of HI is confirmed when all of the following metabolic criteria are present: (1) fasting *and* postprandial hypoglycemia with unsuppressed hyperinsulinism (neonatal hypoglycemia is generally defined as a glucose plasma level of <50 mg/dL after the first 24 h of life with an insulin level >36 pmol/L), (2) suppression of lipolysis and suppression of ketogenesis at the time of the hypoglycemia (lipolysis and hepatic ketogenesis are part of the normal physiologic response to hypoglycemia, and are physiologically inhibited by insulin), and (3) a positive hyperglycemic response to a dose of glucagon, which is a direct insulin antagonist (glucose must increase by 30–50 mg/dL after 0.25–1 mg of intravenous glucagon). Additionally, these criteria must be present for a prolonged period of time and outside certain clinical circumstances such as perinatal stress.

45.5 Classification

45.5.1 Histological Classification

There are two major histological forms of HI: *focal* and *diffuse*, which have a different genetic background and a different management strategy. Focal disease consists of a single focus of adenomatous islet cell hyperplasia surrounded by normal lobular pancreatic tissue. Focal lesions respect the limits of the pancreatic lobules, as opposed to insulinomas which are well demarcated and do not respect the limits of pancreatic lobules. The beta cells within the focal lesion have an enlarged cytoplasm and typically normal nuclei, although some can have nucleomegaly. They accumulate in central clusters, surrounded by non-beta islet cells. The proliferated endocrine cells in the focal lesions push the exocrine components toward the periphery, but there are always some exocrine acinar cells intermixed within the endocrine cells [13]. The size of a focal lesion is variable, from a few millimeters in diameter to much greater than a centimeter. It can be located in the surface of the pancreas, or deep within the organ. Superficial lesions can often be identified visually by subtle differences in color and/or by palpation, since focal lesions tend to be firmer than the normal pancreas. In our experience we have been able to identify the focal lesion by visualization and/or palpation in approximately two-thirds of the cases. Focal lesions can be located anywhere in the pancreas. In our series of more than 140 focal lesions treated by partial pancreatectomy, the distribution was 45% in the pancreatic head, 25% in the neck/body, 15% in the tail, and 15% had "other location", which included focal lesions unusually large that extended beyond a single pancreatic segment, and very rarely lesions that were present within ectopic pancreatic tissue [14]. In the diffuse form of the disease, most, if not all, beta cells are abnormal throughout the organ. The hallmark feature of the beta cells in diffuse HI is the nucleomegaly, which is defined as nuclei that occupy an area three times larger than the nuclei of the adjacent non-beta endocrine cells or four times larger than the nuclei of the adjacent acinar cells. Other nuclear abnormalities (e.g. abnormal shape, pseudoinclusions) may also be present. The total number of endocrine cells in pancreases with diffuse HI is not different than in pancreases from euglycemic age-match individuals. The distribution of the abnormal cells is not always homogeneous. In some cases, cells with clear nucleomegaly can be very concentrated in one area and very sparse in another area of the same specimen, intermixed with beta islet cells that do not look histologically abnormal [15].

Of *all* patients with HI, 30–40% have focal disease and 60–70% have diffuse disease. Among patients who have required surgery at CHOP (which represent approximately 60% of all HI patients), approximately 50% have focal disease and 50% have diffuse disease.

45.5.2 Therapeutic Classification

From a management standpoint, HI is divided in two groups: diazoxide-*responsive* and diazoxide-*resistant*. The initial drug in the management of HI is diazoxide, which inhibits insulin secretion by activating the K-ATP channel. Diazoxide binds to the SUR1 subunit of the channel, but in order to be effective both subunits must be structurally normal and functional. Since the most common causes of HI involve defects in the SUR1/Kir6.2 genes, the majority of HI patients do not respond to diazoxide and the only ones that do are those with mutations in the GK, GDH, SCHAD, or other genes. In our experience with more than 450 patients with HI, only 33% were diazoxide-*responsive,* whereas 67% were diazoxide-*resistant*. Most of diazoxide-*resistant* patients underwent surgery, although some were deemed not candidates for surgery due to a variety of reasons and were managed with different medical strategies [16].

45.6 Genetics

The development of genetic testing and diagnosis has allowed identification of a large number of mutations in patients with HI. To date, about 50%

of patients with HI have a known genetic mutation. The most frequent mutations cause a loss of function in the K-ATP channel of the cytoplasmic membrane of the pancreatic beta cells. This channel is composed of the subunits SUR1 and Kir6.2, which are encoded by two genes located next to each other in the p15.4 region of the chromosome 11: ABCC8 and KCNJ11. The *diffuse* form of HI occurs most frequently as a consequence of mutations of the SUR1/Kir6.2 complex inherited in a recessive manner [17]. There are currently more than 200 known mutations in the ABCC8 and KCNJ11 genes, and some of them have a remarkably high prevalence within certain populations [18]. Very rare mutations of the SUR1 gene inherited in a dominant manner have been identified as a cause of diffuse HI, but the clinical presentation of these patients is milder than patients with recessive disease and they respond partially to diazoxide. In addition, compound heterozygous mutations in the ABCC8/KCNJ11 genes have also been identified as a cause of diffuse HI, but their clinical course is milder [19–21]. Diffuse disease can also occur due to mutations in other genes. Gain-of-function mutations in the GK gene (located in the p15.3-p15.1 region of chromosome 7) inherited in a dominant manner can lead to diffuse HI. Several mutations have been identified already and all affect the same region of the enzyme [10, 11, 22, 23]. A variety of dominant gain-of-function, missense, single-nucleotide mutations in the GDH gene (GLUD1, chromosome 10, region q23.3) have been identified in patients with diffuse HI. These mutations in the GLUD1 gene, as a group, represent the second most frequent cause of HI. All identified mutations affect the GTP-binding site of the enzyme (GTP is the most potent GDH inhibitor) which makes the enzyme work at a higher basal rate [8, 9]. Diffuse HI has also been described as a consequence of recessive mutations in the mitochondrial enzyme short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) gene located in the q22–26 region of chromosome 4. The mutations affect different regions of the protein which explains the heterogeneous clinical presentation of these cases [12, 24]. Over the last few years, cases of diffuse HI have been linked to mutations in three new genes: HNF4A (encoding the hepatocyte nuclear factor 4a; chromosome 20q12–13.1; dominant inheritance), SLC16A1 (encoding the monocarboxylate transporter; chromosome 1p13.2–p12; gain-of-function mutations; dominant inheritance), and UCP2 (encoding the mitochondrial uncoupling protein 2; chromosome 11, region q13; dominant inheritance). Their pathophysiologic mechanisms are not yet well understood, and their age at onset and clinical presentation is variable [25–28].

The *focal* form occurs when an individual with a constitutional paternally inherited mutation in the SUR1/Kir6.2 complex loses the normal maternal allele (an event called "loss of heterozygosity") in a group of pancreatic beta cells (a "two-hit" phenomenon), which not only will oversecrete insulin but will also develop an adenomatous hyperplastic proliferative pattern. The 11p15 region has several genes subject to genomic imprinting. The loss of the maternal 11p15 not only affects the expression of the ABCC8/KCNJ11 genes (not imprinted), but also affects the expression of the maternal tumor suppressor gene H19 and the cell cycle regulator $p57^{kip2}$ (region 11p15.5). The tumor suppressor gene H19 (strongly imprinted and of exclusively maternal monoallelic expression) exerts an antagonistic effect on the insulin-like growth factor 2 (IGF2) expressed exclusively from the paternal allele. The imbalance between IGF2 and H19 is the reason for the adenomatous proliferation of the affected cells. The loss of the maternal allele in a focal lesion can be evidenced by genetic testing and immunohistochemistry (decreased $p57^{kip2}$ staining within the focal lesion) [29]. With regard to the ABCC8/KCNJ11 genes, some cases have only the single abnormal paternal allele, whereas some patients have a duplication of the paternal abnormal allele, which is called uniparental paternal isodisomy.

When a baby is diagnosed with HI in the absence of a family history, the parents and the patient must undergo genetic testing. In cases of diazoxide-*responsive* disease, the genetic testing is not urgent and even with the newest technology can take several weeks. In diazoxide-*resistant* cases, which theoretically have a mutation in the

SUR1/Kir6.2 complex, the genetic testing becomes more critical because it can help in the differential diagnosis of diffuse versus focal disease, determine the need for imaging studies, and provide prognostic information.

45.7 Prenatal Diagnosis and Counseling

The prenatal diagnosis of HI based on the genetic analysis of known mutations in family members is possible, allowing immediate medical management at the time of birth. The genetic mutations that cause diffuse HI respond to the Mendelian inheritance laws with the exception of the *de novo* mutations. For the recessive forms of the HI, the chance of developing the disease in the offspring (homozygous for the affected allele) is 25% for each individual, whereas in cases of dominant inheritance the chance is 50%. Prenatal screening of all known mutations in all HI-involved genes in the general population is not justified by the overall low incidence of the disease, but prenatal diagnosis is justified and currently available for families with previously affected children [30]. While the inheritance of an abnormal ABCC8/KCNJ11 gene from paternal origin does respond to Mendelian laws, the occurrence of focal disease in subsequent siblings of an affected individual is unpredictable given the fact that the second event in the pathogenesis of the disease (the loss of the normal maternal allele) occurs as a random event in somatic cells. The likelihood of this occurrence is extremely low, but it has been described [31].

45.8 Medical Management

The first step in the treatment of newborns with HI is to provide enough glucose to maintain normoglycemia. This is usually achieved by a combination of a high-concentration glucose intravenous infusion plus frequent enteral feeds. The required glucose infusion rate (GIR), calculated as % dextrose × IV rate × 0.169/Wt in kg, can be as high as 25 mg/kg/min which is nearly three times higher than the physiological hepatic glucose release during fasting periods in newborns. Along with supportive glucose management, HI-specific drugs must be initiated. The first line drug is diazoxide. Diazoxide is an agonist of the K-ATP channel and is not effective in patients with recessively inherited mutations in the ABCC8/KCNJ11 complex and severe HI, but it is effective at variable levels in patients with dominant mutations in the ABCC8/KCNJ11 complex, patients with compound heterozygous ABCC8/KCNJ11 mutations, syndromic HI cases (e.g. Beckwith-Wiedeman syndrome) and patients with mutations in most of the other HI-related genes of dominant inheritance known to date. The dose of diazoxide is 5–20 mg/kg/day divided in three oral doses. After 5 days of treatment the response to diazoxide is evaluated by a fasting test, off intravenous glucose and off any other hyperglycemic medications (Fig. 45.2). Patients with the ability to maintain a plasma glucose level >70 mg/dL for at least 12 h are considered diazoxide-*responsive*. For these patients, an adequate feeding regimen is established and they are discharged home on long-term diazoxide treatment. The adverse effects of diazoxide are sodium and fluid retention which can be problematic in patients with concomitant pulmonary or cardiac diseases but can be controlled with the simultaneous administration of diuretics, and hypertrichosis which can be disturbing for the parents but is a benign condition. Patients who cannot maintain glucose levels above 70 mg/dL for 12 h are presumed to have recessively-inherited disease and are considered diazoxide-*resistant*. In these patients, diazoxide is discontinued, the glucose infusion is re-established immediately, and preoperative planning starts. A variety of alternative drugs can be tried in these patients, but mainly as stabilizing agents prior to surgical intervention. Octreotide is a synthetic long-acting somatostatin analog that inhibits insulin secretion by a direct inhibition of voltage-dependent calcium channels. It is generally administered subcutaneously every 6–8 h, but can also be given in a continuous intravenous infusion. The starting dose is 2 μg/kg/day, but it must always be titrated up due to rapid tachyphylaxis. The maximum dose is 15 μg/kg/day. Patients with a partial response to diazoxide

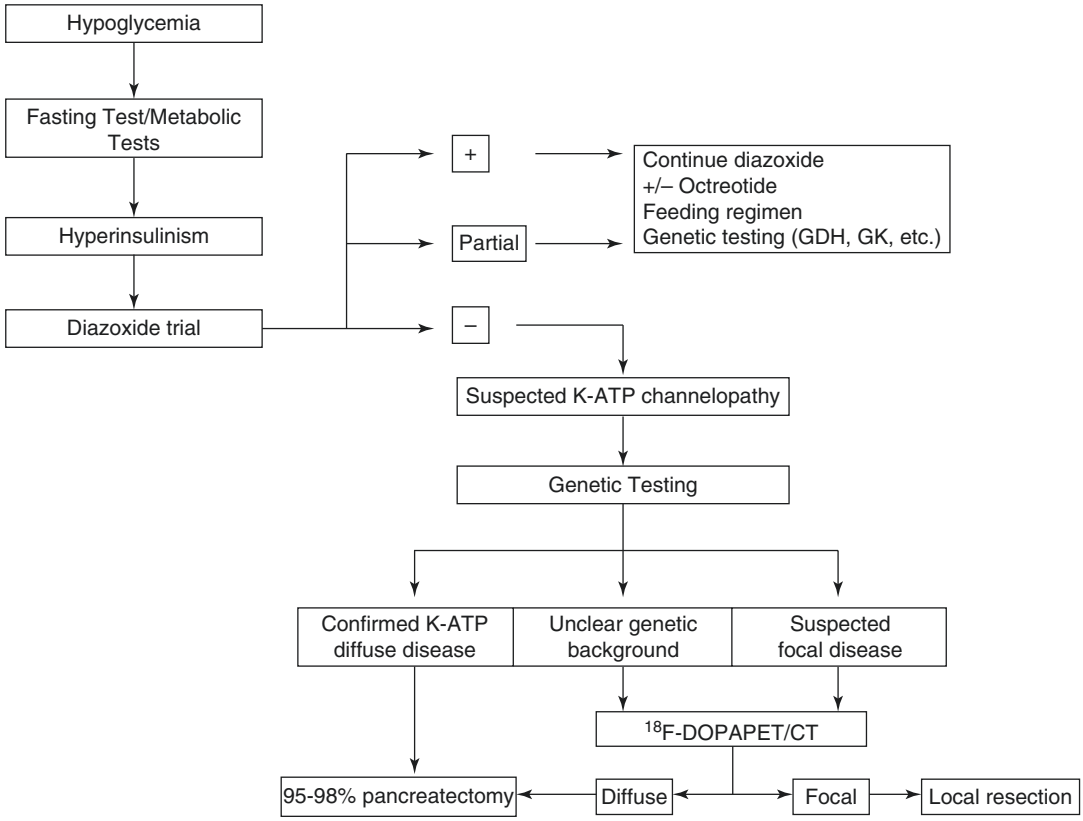

Fig. 45.2 Current algorithm for the management of patients with hyperinsulinism

and some patients with persistent hypoglycemia after a near-total pancreatectomy have been successfully managed at home by a combination of long-term subcutaneous octreotide (twice daily) and a very strict feeding regimen via a gastrostomy. However, octreotide is not recommended for long-term treatment due to its many potential adverse effects (some of which can be life-threatening [e.g. necrotizing enterocolitis]) and its rapid desensitization [32]. Glucagon is a natural insulin antagonist that elevates the plasma glucose levels by activating the enzyme phosphorilase A, which catalyzes the degradation of glycogen. It can be used preoperatively as a continuous intravenous infusion to help maintaining adequate glucose levels or as an intravenous bolus to rescue patients from severe hypoglycemic episodes, but it is not suitable for long-term management. Other drugs, like the calcium channel blocker nifedipine, have been used in the past in the long-term management of patients with HI but their effectiveness is very limited and their use is currently not recommended.

45.9 Preoperative Management

The most relevant aspect of the preoperative planning in patients with diazoxide-*resistant* HI is to differentiate between *diffuse* and *focal* disease, because the surgical strategy is radically different between the two, as is the clinical outcome. Genetic testing is the first step. In the ideal situation, two K-ATP channel mutations are found (one from each parent) confirming diffuse disease, or only one mutation of paternal origin is found, possibly consistent with focal disease. There are situations, however, in which the genetic analysis is difficult to interpret. Sometimes no mutation is found, or in other instances an identified genetic variant is not

disease-causing but simply a rare polymorphism. Additionally, the identification of a mutation in the paternal line does not exclude the possibility of a disease-causing postzygotic mutation on the maternal line (resulting in diffuse HI) not reflected in peripheral blood leukocytes [33].

Patients with genetically confirmed recessive K-ATP-related diffuse disease do not need preoperative imaging and should undergo a near-total pancreatectomy if they cannot be safely managed with medical therapy. The resection of less than 95% of the pancreas is associated with a higher need for another resection and is not recommended [34]. All other patients need preoperative imaging to localize the suspected focal lesion or to help in the differential diagnosis of focal versus diffuse disease when the genetic background is unknown or unclear.

45.10 Imaging Studies

All conventional non-invasive image studies (ultrasound, computerized tomography, magnetic resonance) have been used to try to distinguish between focal and diffuse disease or to localize genetically suspected focal lesions, but these radiologic tests are not helpful. Invasive interventional tests were developed in the late 1980s and were used until 2004 [35, 36]. The Arterial Stimulation with Venous Sampling (ASVS) test measures insulin in the hepatic veins after injecting calcium (a stimulant of insulin release) selectively in the arteries that supply the different regions of the pancreas. An immediate rise in insulin from stimulation in only one artery suggests focal HI in the corresponding area of the pancreas (gastroduodenal artery: pancreatic head; superior mesenteric artery: uncinate process and neck; splenic artery: pancreatic body or tail), whereas an insulin rise in all three areas suggests diffuse HI. The Transhepatic Portal Venous Sampling of the pancreatic veins (THPVS) measures insulin levels in the small pancreatic veins that drain the different regions of the organ to determine if there is an area of higher concentration, consistent with focal disease, or not, consistent with diffuse disease. These techniques take several hours to be performed, are technically very demanding, and their sensitivity and specificity for distinguishing between focal and diffuse disease are limited [37]. They have been largely replaced by what is now considered the gold-standard imaging study: ^{18}fluoro-L-3–4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}FPET/CT). The study was originally developed in the late 1990s for the detection of tumors of neuroendocrine origin in adults, and has been used in HI patients since 2004 [38–40]. Islet cells of the pancreas, like all other neuroendocrine cells, take up L-dihydroxyphenylalanine (L-DOPA), convert it to L-dopamine by the enzyme DOPA decarboxylase, and store it in vesicles. Similarly, these cells can take up ^{18}fluoro-L-3–4 dihydroxyphenylalanine (18FDOPA), convert it into ^{18}fluoro-dopamine and store it in vesicles that can be tracked by their gamma radiation. At CHOP, the isotope ^{18}FDOPA is administered in children under an FDA-approved Investigational New Drug (IND) protocol and the approval of the Institutional Review Board. The isotope has a half-life of 110 min, so it is manufactured on the day of the study in the Cyclotron Facility of the University of Pennsylvania, and used at a dose of 0.08–0.16 mCi/kg (slow intravenous infusion) within 2–3 h of its preparation. All glycemic medications must be stopped prior to the study. The study is done under general anesthesia in a hybrid scanner that initially captures the nuclear signal (γ-radiation) and then generates low-dose (x-radiation) CT scan of the abdomen without changing the patient's position. The nuclear signal is captured at 10-min intervals during only the first 50 min post injection because after that time the tracer accumulates in the liver, gallbladder, biliary tree and duodenal lumen, which can lead to false positive images. Focal lesions are seen as bright spots over a darker background, whereas in cases of diffuse disease the tracer is homogeneously distributed throughout the organ (Fig. 45.3). In our experience with more than 160 studies, the sensitivity of the ^{18}FPET/CT to detect a focal lesion has been 84%. In the 16% that were erroneously diagnosed as diffuse disease, the focal lesions were particularly

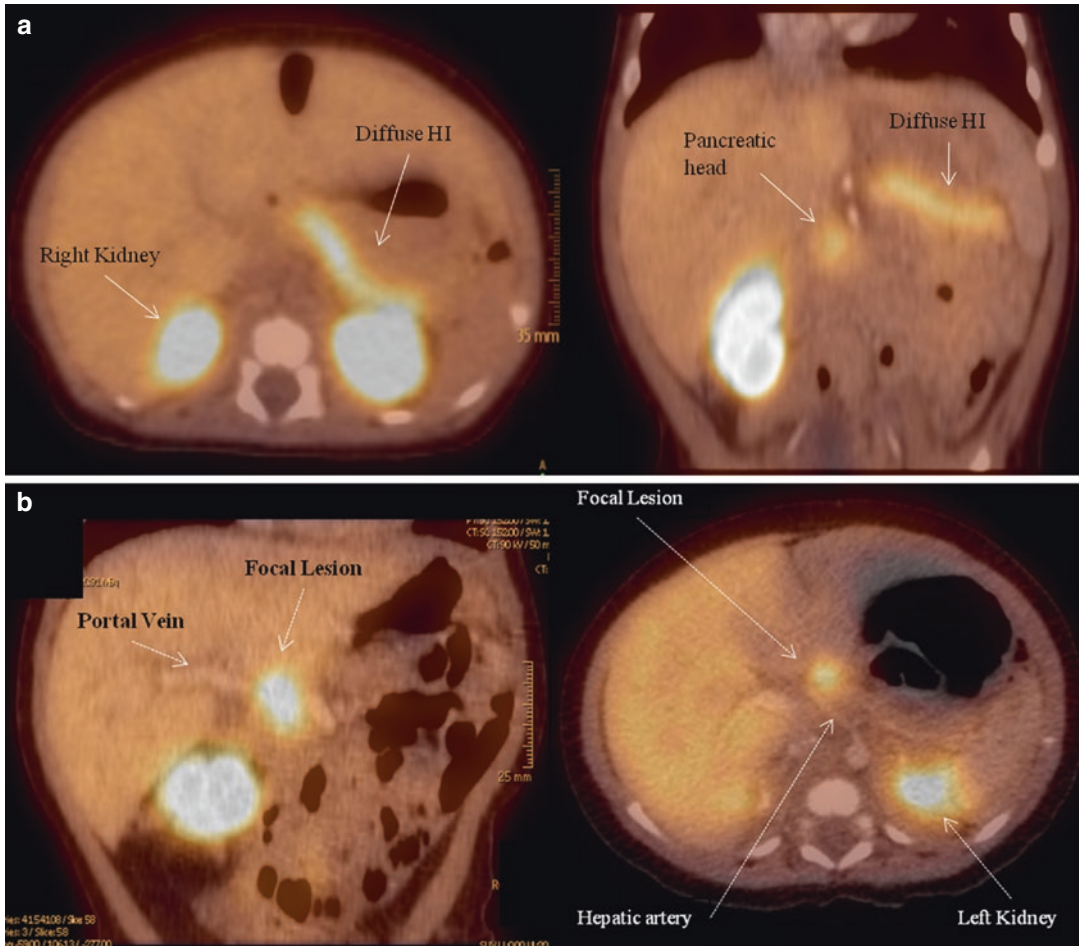

Fig. 45.3 ^{18}Fluoro-L-3–4 dihydroxyphenylalanine positron emission tomography merged with a low-dose radiation computerized tomography (^{18}F-PET/CT). (**a**) Diffuse disease: the entire pancreas uptakes the tracer homogeneously. Coronal and axial views. (**b**) Focal disease: the lesion is a discrete bright spot in the pancreatic head over a darker background. Merging the PET images to the CT images helps to determine the exact location of the focal lesion and its relation to surrounding structures

small (although the size of the lesion does not always correlates with the intensity of the signal), had an unusual shape, or were an atypical case in which the focal lesion occupied most of the pancreas [41]. The ^{18}FPET/CT is also sensitive in the detection of the very rare ectopic focal lesions [14, 42]. When a focal lesion is identified on the ^{18}FPET/CT, the correlation with the actual location determined during the surgery is nearly 100%. In cases with subtle differences in the signal intensity throughout the organ, we do a quantitative activity analysis using the ratio between the peak intensity at the point of interest to the intensity at the background. A ratio $\geq$1.5 is considered diagnostic of focal disease.

45.11 Surgical Management

All open operations are approached using a transverse supraumbilical laparotomy. The pancreas is completely exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the inferior border. It is not necessary to mobilize the spleen. The pancreas is inspected under 3.5X loupe magnification in an attempt to

visualize a focal lesion, and it is also thoroughly palpated. If no focal lesion is identified, then 2-3 mm biopsies are taken from the pancreatic head, body, and tail. Patients with diffuse HI confirmed by intraoperative frozen analysis undergo near-total pancreatectomy. Near-total pancreatectomy (95–98%) involves the resection of the entire pancreas with the exception of a tiny residual piece of pancreatic tissue between the common bile duct and the duodenal wall. The intrapancreatic segment of the common bile duct (CBD) must be completely dissected to perform an for an adequate near-total pancreatectomy. To help with the dissection of the CBD, we place a vessel loop around the extrapancreatic distal CBD and then swing it within the duodenal C-loop to trace the CBD through the head of the pancreas until it enters the duodenum. This maneuver is not needed if the CBD follows a course posterior to the pancreatic head. In children with diffuse disease treated by near-total pancreatectomy, a gastrostomy tube is also placed to provide enteral access for glucose or overnight feeds if needed. When the intraoperative biopsies demonstrate normal pancreatic histology, a further search for the focal lesion using the preoperative localization data is conducted. Intraoperative high-resolution ultrasound has been reported to provide some help in localization because focal lesions may be hypoechoic, but we have been unable to confirm the utility of this radiologic modality [43]. Additional biopsies of suspicious areas are obtained until the focal lesion is identified by frozen section. Expert pediatric pathologic interpretation is vitally important.

Focal lesions tend to be less than 10 mm in diameter (although they can be much larger) and frequently are irregularly shaped. Some lesions have octopus-like extensions that make imperative the intraoperative confirmation of clear margins by frozen section analysis. Focal lesions often have subtle differences in their appearance compared to normal tissue, or may feel firmer than the surrounding normal pancreas. The preoperative PET/CT study greatly facilitates the search. We have been able to identify by visualization and/or palpation approximately two-thirds of all focal lesions. Focal lesions, however, can be buried within the pancreas and be impossible to see or feel. Once the focal lesion is identified, a partial pancreatectomy is performed using frozen sections of margins to ensure a complete resection. Small and superficial lesions in the body or tail can be treated by simple resection. Deep periductal lesions in the body and tail usually are treated by distal pancreatectomy. Superficial and small lesions in the head of the pancreas can also be treated by simple resection. On the other hand, deep pancreatic head lesions close to the common bile duct and pancreatic duct can be tricky to excise completely, particularly if there are tentacles of diseased tissue that emanate from the lesion. To ensure complete lesion resection in these challenging cases, we remove most or all of the pancreatic head, and follow with a Roux-en-Y pancreaticojejunostomy to drain the pancreatic body and tail. By doing this, the endocrine and exocrine functions of the remaining normal pancreas are preserved. In our experience, this approach has been needed in about 40% of focal lesions within the pancreatic head. The end of a retrocolic, 25 cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just *beyond* the cut surface of the pancreas) with fine interrupted 5-O monofilament suture to effectively tuck the cut end of the pancreas into the jejunal lumen (Fig. 45.4). The posterior aspect of the anastomosis is performed first, with all sutures placed first and then tied serially leaving the knots on the inside of the anastomosis, and the anterior aspect is performed last, in the same manner, but leaving the knots on the outside. The omentum is then freed from the transverse colon, wrapped around the anastomosis and sutured into place for additional security. Rarely, a focal lesion in the head will extend into the duodenal wall in which case a Whipple procedure may be needed. In cases of near-total or pancreatic head resections it is important to preserve the gastroduodenal artery as well as the vessels supplying the third and fourth portion of the duodenum (superior and inferior pancreaticoduodenal arteries) to avoid duodenal ischemia [16]. We do not use drains after any pancreatic resection for HI.

We have used laparoscopic surgery in patients with HI. In cases of focal disease of the body or

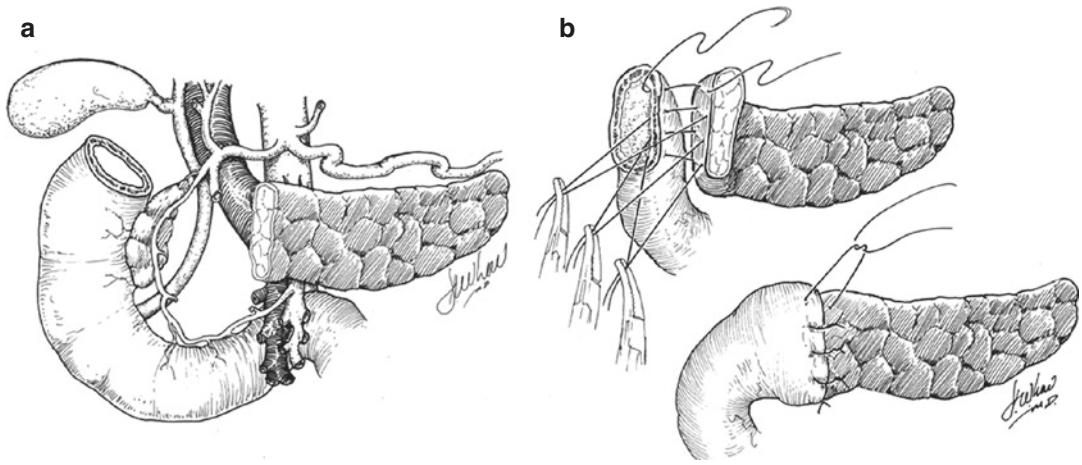

Fig. 45.4 To ensure complete lesion resection of deep pancreatic head lesions close to the common bile duct and pancreatic duct, we remove most or all of the pancreatic head followed by Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail to preserve the endocrine and exocrine functions of the remaining normal pancreas. The end of a retrocolic, 25 cm-long Roux-en-Y jejunal limb is meticulously anastomosed to the capsule of the pancreatic body (just *beyond* the cut surface of the pancreas) to effectively tuck the cut end of the pancreas into the jejunal lumen. The posterior aspect of the anastomosis is performed first, with all sutures placed first and then tied serially leaving the knots on the inside of the anastomosis, and the anterior aspect is performed last, in the same manner, but leaving the knots on the outside. From Laje P, Stanley CA, Palladino AA, et al. Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. J Pediatr Surg, 2012;47 [1]:131–135; used with permission

tail, the approach is straightforward. To facilitate pancreatic body and tail exposure during laparoscopy, it is useful to sew the stomach up to the anterior abdominal wall using 2–3 transabdominal sutures to the anterior gastric wall close to the greater curvature (Fig. 45.5). The carbon dioxide pneumoperitoneum further suspends the stomach anteriorly and also helps to expose the pancreatic body and tail. The laparoscopic procedure is performed via four 3–5 mm ports, and this permits biopsies, complete resection of a visible peripherally located focal lesion, or a distal pancreatectomy if needed. The major drawback to the laparoscopic approach is that there is little tactile feedback to help locate a non-visible focal lesion. Near-total pancreatectomies and pancreatic head resections are significantly more demanding by laparoscopy than by open surgery, and while they are technically feasible, their complication rate such as bleeding and common bile duct injury is higher. The effectiveness of this approach is currently not as good as the open approach given that most reported cases are actually 75—90% pancreatectomies because the CBD is not dissected [44–46]. Perhaps an intraoperative laparoscopic ultrasound probe could facilitate visualization of the CBD to allow precise dissection of this structure.

45.12 Postoperative Management

Postoperative pain is managed by an epidural infusion of bupivacaine, which is kept for 3–4 days, and intravenous narcotics if needed as a continuous infusion or rescue boluses. Patients are kept NPO until bowel function resumes. The intravenous GIR is re-started at a low dose (2 mg/kg/min) because the stress of the surgery induces hepatic glycogenolysis. The GIR is advanced to 5 mg/kg/min 12–18 h after the surgery and to 8 mg/kg/min (equivalent to the physiological hepatic glucose release during fasting periods) 24—36 h after the surgery. Plasma glucose levels are measured hourly in the beginning and spaced out as they become stable. If the plasma glucose levels are excessively high (>400 mg/dL) we assess the presence of ketonic bodies in the urine, and if they are present, an intravenous insulin

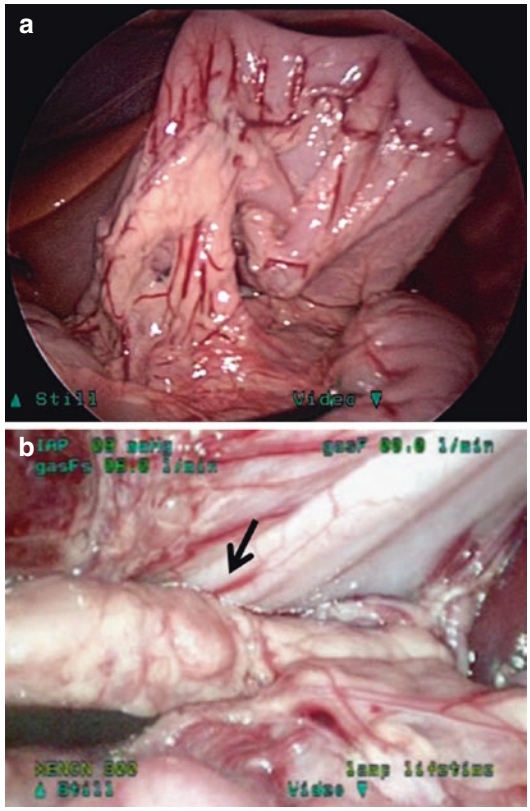

Fig. 45.5 Laparoscopic pancreatectomy. (**a**) To facilitate pancreatic exposure, the stomach is tacked up to the anterior abdominal wall using transabdominal sutures to the anterior gastric wall close to the greater curvature. (**b**) A focal lesion is clearly seen on the anterior-inferior aspect of the pancreatic body. Notice the difference in color between the lesion and the adjacent normal pancreas

infusion is started. The immediate postoperative oscillations in the plasma glucose levels are not reflective of the eventual long-term outcome, because factors like surgical stress and pain can alter glucose homeostasis. When bowel function is evident, enteral feeds are restarted. We start with 1/3 of the goal volume and advance daily by thirds. Simultaneously, the GIR is gradually weaned as the feeding volume increases. When patients are exclusively on enteral feeds, a "cure" fasting test is performed. If patients are able to maintain euglycemia for 18 h, they are considered completely cured. If the time to hypoglycemia is less than 18 h the next step is to determine a regimen of frequent feeds and short fasting periods that will allow the patient to be managed safely at home. Patients that are unable to be weaned from the intravenous glucose infusion rate are obviously not cured and will need further assessment.

45.13 Postoperative Complications

Our overall surgical complication rate after pancreatic surgery for HI is low. General potential complications are bowel obstruction due to adhesions and small intestine to small intestine intussusception (which occurs within the first 2 postoperative weeks) [47]. Specific complications include chyle leaks, pancreatic leaks, and CBD injuries, all of which are very rare in our experience.

45.14 Long-Term Outcomes After Surgery

In our experience with more than 300 pancreatectomies, about 95% of patients with focal disease are cured after surgery. The remaining 5% require some degree of support that is usually consists of a strict feeding regimen, and these cases are presumed to be secondary to microscopic residual disease. In cases of diffuse HI, approximately 50% of cases continue to have hypoglycemia after surgery and may require supportive management with octreotide and frequent feeds, and 25% develop diabetes requiring insulin. These patients, despite not being cured, are much easier to manage than before the surgery. Finally, approximately 25% of diffuse HI cases are well controlled with no medications. Long term follow-up is mandatory since insulin-dependent diabetes can develop even a decade, or more, later.

References

1. Stanley CA. Hyperinsulinism in infants and children. Pediatr Clin North Am. 1997;44:363–74.
2. Arnoux JB, de Lonlay P, Ribeiro MJ, et al. Congenital hyperinsulinism. Early Hum Dev. 2010;86(5):287–94.
3. McQuarrie I. Idiopathic spontaneously occurring hypoglycemia in infants; clinical significance of problem and treatment. Am J Dis Child. 1954;87(4):399–428.

4. Graham EA, Hartmann AF. Subtotal resection of the pancreas for hypoglycaemia. Surg Gynecol Obstet. 1934;59:474–9.
5. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest. 1960;39:1157–75.
6. Yakovac WC, Baker L, Hummeler K. Beta Cell nesidioblastosis in idiopathic hypoglycemia of infancy. J Pediatr. 1971;79(2):226–31.
7. Rahier J, Fält K, Müntefering H, et al. 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.
8. Palladino AA, Stanley CA. The hyperinsulinism/hyperammonemia syndrome. Rev Endocr Metab Disord. 2010;11(3):171–8.
9. Stanley CA. Two genetic forms of hyperinsulinemic hypoglycemia caused by dysregulation of glutamate dehydrogenase. Neurochem Int 2010 2. 2011;59(4):465–72.
10. Kassem S, Bhandari S, Rodríguez-Bada P, et al. Large islets, beta-cell proliferation, and a glucokinase mutation. N Engl J Med. 2010;362(14):1348–50.
11. Glaser B, Kesavan P, Heyman M, et al. Familial hyperinsulinism caused by an activating glucokinase mutation. N Engl J Med. 1998;338(4):226–30.
12. Li C, Chen P, Palladino A, et al. Mechanism of hyperinsulinism in short-chain 3-hydroxyacyl-CoA dehydrogenase deficiency involves activation of glutamate dehydrogenase. J Biol Chem. 2010;285(41):31806–18.
13. Rahier J, Guiot Y, Sempoux C. Morphologic analysis of focal and diffuse forms of congenital hyperinsulinism. Semin Pediatr Surg. 2011;20(1):3–12.
14. Peranteau WH, Bathaii SM, Pawel B, et al. Multiple ectopic lesions of focal islet adenomatosis identified by positron emission tomography scan in an infant with congenital hyperinsulinism. J Pediatr Surg. 2007;42(1):188–92.
15. Suchi M, MacMullen C, Thornton PS, et al. Histopathology of congenital hyperinsulinism: retrospective study with genotype correlations. Pediatr Dev Pathol. 2003;6(4):322–33.
16. Laje P, Stanley CA, Palladino AA, et al. Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism. J Pediatr Surg. 2012;47(1):131–5.
17. 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(11):752–9.
18. Flanagan SE, Clauin S, Bellanné-Chantelot C, et al. Update of mutations in the genes encoding the pancreatic beta-cell K(ATP) channel subunits Kir6.2 (KCNJ11) and sulfonylurea receptor 1 (ABCC8) in diabetes mellitus and hyperinsulinism. Hum Mutat. 2009;30:170–80.
19. 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(7):897–906.
20. 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.
21. Dekel B, Lubin D, Modan-Moses D, et al. Compound heterozygosity for the common sulfonylurea receptor mutations can cause mild diazoxide-sensitive hyperinsulinism. Clin Pediatr. 2002;41:183–6.
22. Dullaart RP, Hoogenberg K, Rouwe CW, et al. Family with autosomal dominant hyperinsulinism associated with A456V mutation in the glucokinase gene. J Intern Med. 2004;255:143–5.
23. 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.
24. 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(1):221–7.
25. González-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(12):e3850.
26. 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.
27. Flanagan S, Kapoor R, Mali G, et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur J Endocrinol. 2010;162:987–92.
28. Marquard J, Palladino AA, Stanley CA, et al. Rare forms of congenital hyperinsulinism. Semin Pediatr Surg. 2011;20(1):38–44.
29. Suchi M, MacMullen CM, Thornton PS, et al. Molecular and immunohistochemical analyses of the focal form of congenital hyperinsulinism. Mod Pathol. 2006;19(1):122–9.
30. Peranteau WH, Ganguly A, Steinmuller L, et al. Prenatal diagnosis and postnatal management of diffuse congenital hyperinsulinism: a case report. Fetal Diagn Ther. 2006;21(6):515–8.
31. Ismail D, Smith VV, de Lonlay P, et al. Familial focal congenital hyperinsulinism. J Clin Endocrinol Metab. 2011;96(1):24–8.
32. Laje P, Halaby L, Adzick NS, et al. Necrotizing enterocolitis in neonates receiving octreotide for the management of congenital hyperinsulinism. Pediatr Diabetes. 2010;11:142–7.
33. Palladino AA, Stanley CA. A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism. Semin Pediatr Surg. 2011;20(1):32–7.
34. Lovvorn HN 3rd, Nance ML, Ferry RJ Jr, et al. Congenital hyperinsulinism and the surgeon: lessons learned over 35 years. J Pediatr Surg. 1999;34(5):786–92.

35. Doppman JL, Miller DL, Chang R, et al. Insulinomas: localization with selective intraarterial injection of calcium. Radiology. 1991;178(1):237–41.
36. Brunelle F, Negre V, Barth MO, et al. Pancreatic venous samplings in infants and children with primary hyperinsulinism. Pediatr Radiol. 1989;19(2):100–3.
37. Adzick NS, Thornton PS, Stanley CA, et al. A multidisciplinary approach to the focal form of congenital hyperinsulinism leads to successful treatment by partial pancreatectomy. J Pediatr Surg. 2004;39(3):270–5.
38. Hoegerle S, Schneider B, Kraft A, et al. Imaging of a metastatic gastrointestinal carcinoid by F-18-DOPA positron emission tomography. Nuklearmedizin. 1999;38(4):127–30.
39. 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(4):560–6.
40. 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(1):13–8.
41. 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(12):4706–11.
42. Hussain K, Seppänen M, Näntö-Salonen K, et al. The diagnosis of ectopic focal hyperinsulinism of infancy with [18F]-dopa positron emission tomography. J Clin Endocrinol Metab. 2006;91(8):2839–42.
43. von Rohden L, Mohnike K, Mau H, et al. Visualization of the focus in congenital hyperinsulinism by intraoperative sonography. Semin Pediatr Surg. 2011;20(1):28–31.
44. Bax NM, van der Zee DC, de Vroede M, et al. Laparoscopic identification and removal of focal lesions in persistent hyperinsulinemic hypoglycemia of infancy. Surg Endosc. 2003;17(5):833.
45. Al-Shanafey S. Laparoscopic vs open pancreatectomy for persistent hyperinsulinemic hypoglycemia of infancy. J Pediatr Surg. 2009;44(5):957–61.
46. Pierro A, Nah SA, et al. Surgical management of congenital hyperinsulinism of infancy. Semin Pediatr Surg. 2011;20(1):50–3.
47. Laje P, Stanley CA, Adzick NS. Intussusception after pancreatic surgery in children: a case series. J Pediatr Surg. 2010;45(7):1496–9.