Congenital Hyperinsulinism

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In 1934, Evarts Graham from St. Louis, MO performed the first successful pancreatectomy on a child with HI. The pancreas was explored searching for an adenoma, but since no adenoma was found a subtotal pancreatectomy (~90 %) was performed and the patient's hypoglycemia resolved. This was done 20 years before the first description of HI, which was initially termed "syndrome of idiopathic hypoglycemia of infants." It was initially believed that HI was caused by an over-secretion of insulin secondary to an abnormally high number of pancreatic islets resulting from an anomalous phenomenon of postnatal budding of endocrine cells of the pancreatic ducts called nesidioblastosis (*nesidion* means "island"). This theory was based on the histologic analysis of pancreatic specimens from children with HI stained with insulin-specific techniques. Later studies showed that nesidioblastosis was a normal neonatal phenomenon and thus this term is no longer used. Recent advances in molecular diagnosis have conclusively demonstrated that HI does not result from a developmental abnormality but from a variety of genetic derangements that alter the regulatory mechanisms of insulin secretion and glucose homeostasis.

Histological Classification

There are two major histological forms of HI: focal and diffuse (Fig. 84.1). They differ significantly in terms of genetic basis, management strategy, and surgical approach. Focal HI consists of a focus of adenomatous islet cell hyperplasia surrounded by normal pancreatic tissue. Focal lesions retain the lobular architecture of the normal pancreas in contrast to insulinomas, which do not. The beta cells within the focal lesion have an enlarged cytoplasm and typically normal nuclei, although nucleomegaly is not uncommon. Beta cells accumulate in clusters surrounded by non-beta islet cells. The exocrine and canalicular cells are pushed toward the periphery, but are always somewhat intermixed within the endocrine cells. Focal lesions vary in size from a few millimeters to greater than a centimeter or much more, and can be superficial or deep. In our series of more than 200 operated focal lesions, 45 % were located in the pancreatic head, 25 % in the neck/body, 15 % in the tail, and 15 % in other locations that included unusually large lesions that extended beyond a single pancreatic segment, and very rarely lesions located in ectopic pancreatic tissue.

Diffuse HI, on the other hand, has one primary histological hallmark feature that distinguishes it from a normal pancreas: beta cell nucleomegaly. Nucleomegaly 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. In the vast majority of cases of diffuse HI, the abnormal beta cells are distributed homogeneously throughout the pancreas, and the total number of beta cells is normal.

Of all patients with HI, 30–40 % have focal disease and 60–70 % have diffuse disease. In our experience of more than 400 HI patients who underwent surgery since 1999, 53 % had focal disease and 47 % had diffuse disease.

There are rare histological forms of HI that are neither focal nor diffuse, and are called "atypical." Among these are focal lesions that occupy a large segment of the pancreas, cases of remarkable endocrine hyperplasia in patients with Beckwith–Wiedemann syndrome, and cases with features of diffuse HI restricted to a single area of the pancreas, or distributed in a mosaic pattern (Localized Islet Nuclear Enlargement, LINE). Patients with atypical forms of HI are clinically heterogeneous and require a medical and surgical management individually crafted according to the severity of each case.

Pathogenesis and Genetics

When the plasma glucose concentration rises, glucose enters into the beta cell and initiates a chain of events that results in prompt insulin secretion. The metabolism of glucose molecules

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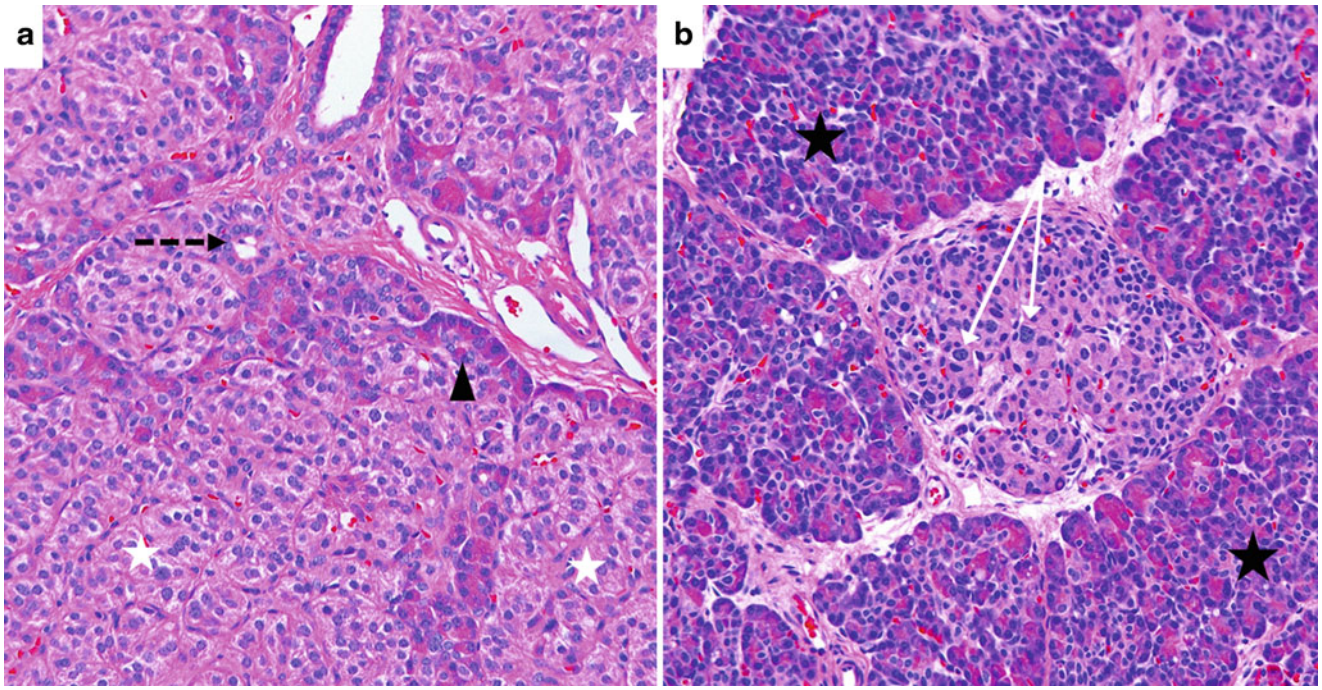

Fig. 84.1 Histology of HI. (**A**) Focal lesion. There is hyperplasia of beta cells (*white stars*), with exocrine (*black arrowhead*) and ductal (*black arrow*) components within the lesion. (**B**) Diffuse HI. Endocrine cells show nucleomegaly (*white arrows*) within an otherwise normal islet of Langerhans. The exocrine component is normal (*black stars*)

inside the beta cell derives in the conversion of ADP into ATP, elevating the ATP:ADP ratio. As a consequence, the ATP-dependent potassium (K-ATP) channels of the cell membrane become inactive and close, potassium accumulates on the inner surface of the cell membrane and depolarizes it, the depolarization of the cell membrane activates the voltage-dependent calcium channels, and calcium enters the cell, accumulates in the cytoplasm, and triggers a calcium-dependent insulin exocytosis. When the K-ATP channel is defective due to loss-of-function genetic mutations it remains closed at all times regardless of the plasma glucose level, generating a non-regulated, persistent insulin release that leads to hypoglycemia. This is the most common pathophysiologic mechanism of HI. Insulin levels, however, are never strikingly elevated in HI.

The K-ATP channel of the beta cell membrane is composed of the subunits "SUR1" (a sulfonylurea receptor, the regulatory subunit) and "Kir6.2" (the ion pore), which are, respectively, coded by two genes located next to each other in the p15.4 region of the chromosome 11: ABCC8 and KCNJ11. There are currently more than 200 known mutations in the ABCC8 and KCNJ11 genes, and about 50 % of all patients with HI have a known mutation, which means that it was identified in previous HI patients. The diffuse form of HI occurs most frequently due to homozygous mutations of the SUR1/Kir6.2 complex inherited in an autosomal recessive manner. Rarely, mutations of the ABCC8 and KCNJ11 genes are inherited in a dominant manner, and compound heterozygous ABCC8/KCNJ11 mutations cause diffuse HI. The clinical presentation of these patients is milder than patients with homozygous recessive disease. Diffuse HI can also occur due to mutations in the genes of six other enzymes and metabolic factors: glucokinase (GK, 7p15.3-p15.1), glutamate dehydrogenase (GDH, 10q23.3, "hyperinsulinism-hyperammonemia syndrome"), short-chain hydroxyacyl-CoA dehydrogenase (SCHAD, 4q22–26), hepatocyte nuclear factor 4a (HNF4A, 20q12–13.1), monocarboxylate transporter 1 (MCT1, 1p13.2–p12), and the uncoupling protein 2 (UCP2, 11q13).

The focal form of HI occurs through a "two-hit" phenomenon: for the first "hit," the individual inherits a mutation in the paternal allele of the SUR1/Kir6.2 complex, and for the second "hit," the maternal 11p15 region containing the normal maternal allele is lost in a single pancreatic beta cell. The loss of the maternal 11p15 region is a completely random event that has no inheritable component. This event is called "loss of heterozygosity" in which the allele from only one progenitor is present, and the other allele is lost. The affected beta cell not only will oversecrete insulin, but will also develop an adenomatous hyperplastic proliferation due to an imbalance in a series of genes that regulate cell proliferation that are also contained in the 11p15 region and are subject to genomic imprinting. The 11p15 region contains the tumor suppressor gene H19 and the cell cycle regulator $p57^{kip2}$. H19 is strongly imprinted and of exclusively maternal monoallelic expression, and exerts an antagonistic effect

on the insulin-like growth factor 2 (IGF2) expressed from the paternal allele. The imbalance between IGF2 and H19 is the reason for the adenomatous proliferation of the affected beta cells, the so-called focal lesion.

When a baby is diagnosed with HI in the absence of a family history, the parents and the patient should undergo genetic testing. In medically responsive HI, the genetic testing has only a diagnostic purpose. On the other hand, in medically resistant cases the genetic testing becomes more relevant since it can help differentiate between diffuse and focal HI, determine the need for imaging studies, determine the surgical approach, and provide prognostic information.

Diagnosis

The diagnosis of HI is established through a series of simple blood tests. The following three metabolic criteria must be present to confirm HI: (1) fasting and postprandial hypoglycemia with unsuppressed hyperinsulinism in which neonatal hypoglycemia is defined as a glucose plasma concentration of <50 mg/dL after the first 24 h of life, with a simultaneous plasma insulin concentration of >36 pmol/L; (2) suppression of lipolysis and suppression of ketogenesis at the time of the hypoglycemia because lipolysis and hepatic ketogenesis are a normal physiologic response to hypoglycemia, and are physiologically inhibited by insulin; and (3) a positive glycemic response to a dose of glucagon, which is a direct insulin antagonist, such that glucose must increase by 30–50 mg/dL after 0.25–1 mg of intravenous glucagon. The three criteria must be present for a prolonged period of time and outside clinical circumstances such as perinatal stress and sepsis.

The mainstay drug in the treatment of HI is diazoxide, which inhibits insulin secretion by activating the K-ATP channel. Diazoxide binds to the SUR1 subunit of the K-ATP channel and keeps it open, but in order to be effective both subunits of the channel must be structurally and functionally normal. From a therapeutic standpoint HI is divided into two groups: diazoxide-responsive and diazoxide-resistant. Since the most common cause of HI is a mutation in the SUR1/Kir6.2 gene complex, the majority of HI patients do not respond to diazoxide. The ones that do respond are those with mutations in the GK, GDH, SCHAD, and other HI-related genes. In our experience treating over 600 HI patients, about 1/3 of them were diazoxide-responsive and 2/3 were diazoxide-resistant. Diazoxide-resistant patients generally require surgery.

Prenatal Diagnosis and Counseling

Prenatal screening of all known mutations of all HI-related genes in the general population is impractical due to the low incidence of the disease. On the other hand, prenatal diagnosis in families with affected probands is possible and justified because it allows immediate postnatal management. In the case of diffuse HI, the genetic mutations follow principles of Mendelian inheritance—the chance of diffuse HI in the offspring of carrier parents is 25 %. In the case of focal HI, on the other hand, while the inheritance of a paternal ABCC8/KCNJ11 mutation follows Mendelian laws, the development of a focal lesion in subsequent siblings of an affected individual is completely unpredictable given the fact that the second event in the pathogenesis of the disease (the loss of the normal maternal allele) is a random non-inheritable event that occurs in a single somatic cell. The likelihood of focal HI in siblings is exceedingly low, but has been reported.

Medical Management

The priority in the treatment of babies with HI is to prevent hypoglycemia, because it can lead to irreversible brain damage. This is achieved by a combination of a high-concentration intravenous glucose infusion and frequent enteral feeds. The required glucose infusion rate (GIR), calculated as % dextrose × IV rate × 0.169/weight in kg, may need to be as high as 30 mg/kg/min, which is more than three times the physiological hepatic glucose release rate observed in newborns during fasting periods. In addition to glucose administration, hyperglycemic drugs must be initiated as soon as possible. The first line drug is diazoxide. Diazoxide is not effective in patients with recessively inherited mutations in the ABCC8/KCNJ11 gene complex, but it can be partially effective in patients with dominant and compound heterozygous mutations. Diazoxide is effective in patients with mutations in all the other HI-related genes of dominant inheritance known to date. After five consecutive days of diazoxide administration the response is evaluated by a fasting test during which glucose infusion and all medications must be stopped. Patients who can maintain a plasma glucose level of >70 mg/dL for 12 h or more are considered diazoxide-responsive. These patients are subsequently managed by a regimen of frequent feedings and long-term diazoxide (Fig. 84.2). Diazoxide causes sodium and water retention, which can be controlled with diuretics, and hypertrichosis.

Patients whose plasma glucose level falls below 70 mg/dL within the first few hours of the fasting test are considered diazoxide-resistant and are presumed to have ABCC8/KCNJ11-related HI. These patients resume the glucose intravenous infusion immediately and start a preoperative work-up. Patients who are able to maintain the plasma glucose level above 70 mg/dL for several hours but do not reach the 12-h mark are considered to have a partial response to diazoxide, and are managed with a combination of diazoxide and continuous (or very frequent) feedings.

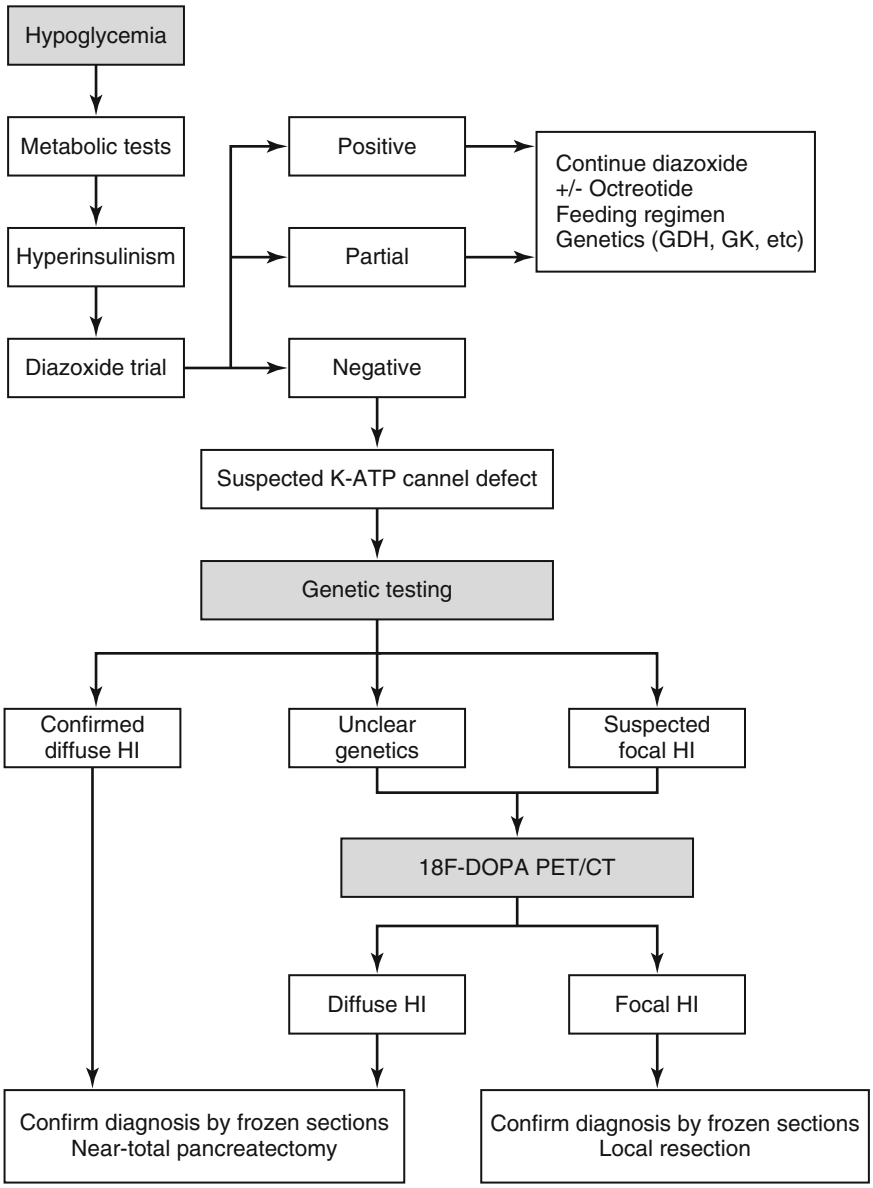

Fig. 84.2 Management algorithm for patients with HI

In patients with diazoxide-resistant HI, alternative drugs can be used to maintain euglycemia prior to surgical intervention. Those drugs include octreotide and glucagon. 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, or as a continuous subcutaneous infusion. The dose must always be titrated up due to rapid tachyphylaxis. Glucagon is a natural insulin antagonist that is mainly used to promptly reverse severe hypoglycemic episodes.

Patients with a partial response to diazoxide and patients with persistent hypoglycemia after a near-total pancreatectomy who cannot be re-operated on can potentially be managed at home with a long-term subcutaneous octreotide administration. However, the long-term use of octreotide has several concerning aspects: (1) octreotide has potential adverse effects (splanchnic ischemia), (2) octreotide receptors desensitize rapidly, and (3) octreotide interferes with other endocrine pathways (growth hormone). Other somatostatin analogues with different pharmacokinetic profiles have been used as long-term therapies in patients with diazoxide-resistant HI (a slow-release gel formulation of lanreotide administered once a month), but the experience is anecdotal. Similarly, there are anecdotal cases of HI patients treated with the immunosuppressant sirolimus.

Preoperative Management

The most important aspect of the preoperative planning is to determine whether the patient has diffuse or focal disease, because the surgical strategy is radically different between

the two. Genetic testing is the first step (Fig. 84.2). Ideally, either a known disease-causing K-ATP channel mutation is found on the maternal and paternal alleles, confirming recessive diffuse HI, or only one disease-causing mutation is found in the paternal allele, suggesting focal disease. The identification of only a mutation in the paternal allele does not exclude the rare possibility of a diffuse-HI-causing postzygotic mutation on the maternal allele, which would not be detected by peripheral blood leukocyte genetic testing. Occasionally, a previously unknown genetic variant is found. In those cases it is impossible to determine if it is a new disease-causing mutation or simply a rare polymorphism.

Patients with genetically confirmed recessive K-ATP-related diazoxide-resistant diffuse HI do not need preoperative imaging studies and nearly always require a near-total pancreatectomy. Resection of <95 % of the pancreas is associated with a high failure rate and need for further resection. Patients with genetic testing suggestive of focal HI must undergo imaging studies to confirm focal disease and to localize the suspected lesion (Fig. 84.2). When the genetic background is unknown or unclear, the patient should undergo imaging studies to determine if it is a case of focal or diffuse HI.

Imaging

Conventional non-invasive imaging studies such as transabdominal US, CT, and MRI are not helpful to distinguish between focal and diffuse HI or to localize focal lesions. Invasive interventional tests developed in the 1990s (arterial stimulation/venous sampling, and transhepatic portal venous sampling) are somewhat helpful, but they take several hours to be performed, are technically very demanding, and a large amount of blood needs to be withdrawn from the patient to obtain relevant data. Those studies have been largely replaced by what is now considered the standard imaging study for HI: ^{18}Fluoro-L-3-4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation CT (^{18}F-PET/CT). Islet cells of the pancreas 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 (^{18}F-DOPA), convert it into ^{18}fluoro-dopamine, and store it in vesicles that can be tracked by their gamma radiation.

We administer the ^{18}F-DOPA under an FDA-approved Investigational New Drug protocol with the approval of our IRB. The ^{18}F-DOPA has a half-life of 110 min and is manufactured on the day of the study in the Cyclotron Facility of the University of Pennsylvania. The study is done under general anesthesia in a PET/CT hybrid scanner that initially captures the radioactive signal and then generates a low-radiation CT scan of the abdomen, without moving the patient. Focal lesions (which represent hyperplastic adenomatosis of beta cells) are seen as bright spots over a dark background due to the high concentration of the tracer, whereas in cases of diffuse disease the tracer is homogeneously distributed throughout the organ (Fig. 84.3). The sensitivity of the ^{18}F-PET/CT to detect a focal lesion is 85 % and the correlation between the location on the

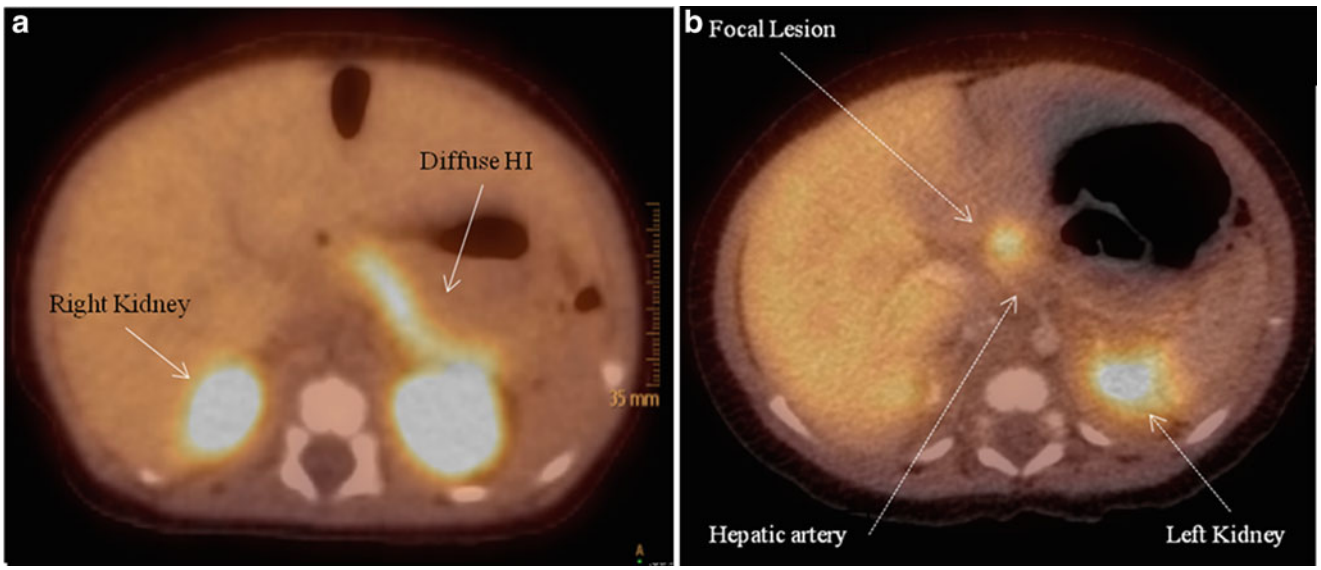

Fig. 84.3 ^{18}Fluoro-L-3-4 dihydroxyphenylalanine positron emission tomography merged with a low-radiation computerized tomography (^{18}F-PET/CT). (**A**) Diffuse HI: the entire pancreas takes up the tracer homogeneously. (**B**) Focal HI: the lesion is a discrete bright spot in the pancreatic head

images and the location at surgery is nearly 100 %. The ^{18}F-PET/CT is also sensitive in the detection of the very rare ectopic focal lesion.

Surgical Management

The operation is done through 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 of the pancreas. The pancreas is inspected with 4X loupe magnification and carefully palpated to identify a focal lesion. Focal lesions are often firmer than the normal pancreatic tissue and may have subtle differences in appearance and texture. If no obvious focal lesion is identified, tiny biopsies are taken sharply (cautery is avoided because it hampers frozen section pathology interpretation) from the pancreatic head, body, and tail for intraoperative frozen section analysis.

If diffuse HI is confirmed, the patient undergoes a near-total pancreatectomy, which involves resection of the entire pancreas leaving only a tiny residual piece of pancreatic tissue between the common bile duct and the duodenal wall. The intrapancreatic segment of the CBD must be identified and skeletonized. To help with the identification and dissection of the CBD when it is embedded in the pancreatic head, we place a vessel loop or two around the extrapancreatic section of the CBD posterior to the duodenum and then swing it medially within the duodenal C-loop. This maneuver is not needed if the CBD follows a visible course completely posterior to the pancreatic head. In babies with diffuse disease we place a gastrostomy for long-term enteral access.

If intraoperative biopsies confirm normal pancreatic histology on the random biopsies of the head, body, and tail, a further search for the focal lesion is conducted. The preoperative PET/CT study greatly facilitates the search. Intraoperative high-resolution US can help in localizing focal lesions and we routinely arrange for this if the genetics suggest a focal lesion but the PET/CT does not show it, which occurs in 15 % of cases. We have been able to identify by 4X loupe magnification visualization or palpation approximately two-thirds of all focal lesions. Focal lesions that are buried within the pancreatic tissue can be impossible to see or feel, so it is necessary to patiently take additional biopsies of suspicious areas for frozen section analysis until the lesion is found.

Expert pediatric anatomic pathology interpretation is crucial. Focal lesions are generally less than 10 mm in diameter, but can be much larger. They are irregularly shaped and frequently have octopus-like tentacles, which make the intraoperative frozen section confirmation of clear margins imperative. Once the focal lesion is identified, a partial pancreatectomy is performed (free-of-disease margins must be confirmed before concluding the surgery). Small and superficial lesions in the body or tail can be treated by simple resection, and intraoperative ultrasound can visualize the relationship of the less than 0.5 mm diameter pancreatic duct to the focal lesion. Deep periductal lesions in the body and tail 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 lesions of the pancreatic head can be difficult to excise with clear margins without causing damage to the CBD or pancreatic duct. To ensure a complete resection of the lesion in these challenging cases, we remove almost all the pancreatic head and construct a Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail, thereby preserving the endocrine and exocrine functions of the pancreas. This approach is required in about 40 % of focal lesions located in 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 end of the pancreas) with fine interrupted monofilament suture to tuck the cut end of the pancreas into the jejunal lumen (Fig. 84.4). The omentum is then wrapped around the anastomosis in case of an anastomotic leak. 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 and pancreatic head resections it is crucial to preserve the gastroduodenal artery as well as the vessels supplying the third and fourth portion of the duodenum (superior/inferior posterior/anterior pancreaticoduodenal arteries), if possible, to avoid duodenal ischemia. Either the monopolar or bipolar cautery can be used to take the tiny pancreatic venous branches that drain into the splenic vein and take the splenic arterial branches to the pancreas. We do not routinely use drains after any pancreatic resection for HI.

Laparoscopic surgery is particularly suitable in HI patients with focal disease of the pancreatic body or tail. We use three or four 3–5 mm ports and to facilitate pancreatic exposure the stomach is tacked up to the anterior abdominal wall with 2–3 transabdominal-transgastric stitches near the greater curvature. A major drawback to the laparoscopic approach is the very limited tactile feedback to help palpate a non-visible focal lesion. The dissection and resection of the pancreatic head is more technically demanding than the distal pancreas. A high rate of CBD injury has been observed in cases of laparoscopic near-total pancreatectomies in which the CBD is identified and dissected laparoscopically. Recent reports claim a lower rate of CBD injuries, but a detailed analysis reveals that in those cases the CBD is neither identified nor dissected and the pancreatectomy ends just beyond the superior mesenteric vessels, which means that those cases are not near-total but rather subtotal or distal pancreatectomies with an attendant risk of difficult to manage postoperative hypoglycemia.

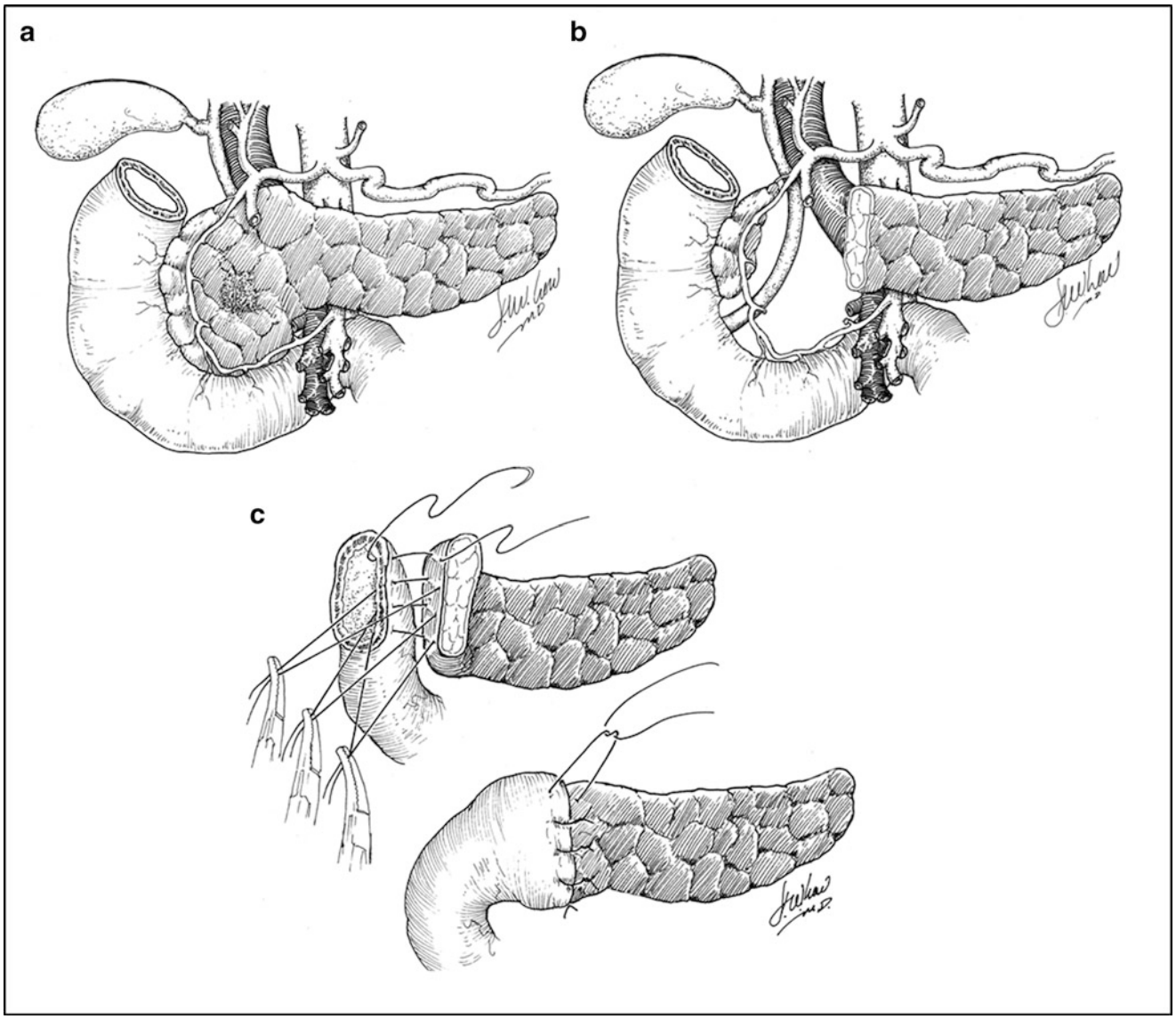

Fig. 84.4 (**A**) Focal lesion in the head of the pancreas that has octopus-like tentacles that extend into the normal tissue. (**B**) Near-total pancreatic head resection. The common bile duct (CBD) is skeletonized and the duodenal vasculature is preserved. A tiny portion of the pancreatic head is left between the CBD and the duodenal wall. (**C**) Pancreaticojejunostomy. Fine interrupted monofilament stitches are placed from the end of the jejunal limb (full thickness) to the capsule of the pancreas just beyond the cut edge so that the cut end of the pancreatic body is tucked 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. The anterior aspect is performed in the same manner, but leaving the knots on the outside. From Laje et al: *Pancreatic head resection and Roux-en-Y pancreaticojejunostomy for the treatment of the focal form of congenital hyperinsulinism*. (Reproduced from 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 Ped Surg. 2012; 47(1): 130–135, with permission from Elsevier.)

Postoperative Management

Postoperative pain after pancreatectomy is managed by an epidural catheter or intravenous narcotics. Patients are kept NPO until bowel function resumes. The intravenous glucose infusion is re-started immediately after the operation at a low GIR (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 if they are stable. If the plasma glucose levels are excessively high (>400 mg/dL), then an intravenous insulin infusion is started. The immediate postoperative oscillations in the plasma glucose levels do not predict the eventual long-term outcome, because factors like surgical stress and pain can alter glucose

homeostasis. When bowel function is evident, enteral feedings are resumed and the intravenous glucose infusion is gradually weaned off. 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 who are unable to be weaned from the intravenous GIR are not cured and will need further assessment to determine if additional surgery or medical management is required.

Outcomes

In our experience, patients with focal HI are cured with the surgery in more than 95 % of the cases. The outcome of patients with diffuse HI who undergo a near-total pancreatectomy is less predictable. In our experience, approximately 50 % of cases continue to have hypoglycemia after surgery and require supportive management with frequent or even continuous feeds. Despite this less-than-ideal outcome, these patients are much more easily manageable after surgery than before the operation and are at home off intravenous infusions. Approximately 25 % of patients who undergo near-total pancreatectomy achieve normoglycemia and do not require any additional therapy. Lastly, approximately 25 % of cases develop early diabetes requiring insulin. Recent studies have shown that the incidence of insulin-dependent diabetes increases with time, to reach more than 90 % ten years after the operation. The long-term incidence of clinically evident exocrine insufficiency is as high as 50 %.

Editor's Comment

The pediatric surgeon must be aware of the immediate management and differential diagnosis for newborns with persistent hyperglycemia. Infants with hyperinsulinism should be managed very aggressively with high-dose intravenous glucose infusions oftentimes necessitating central venous access. The long-term profound neurodevelopmental sequelae secondary to hypoglycemia can be devastating and irreversible and thus a systematic multidisciplinary treatment strategy between neonatologists, endocrinologists, and surgeons must be clearly defined.

Diffuse disease is treated with a near-total (95–98 %) pancreatectomy. Focal disease is treated by complete resection of the tumor with negative margins. Classically described interventional radiology studies such as arterial stimulation with venous sampling or hepatic portal venous catheterization and selective sampling of the pancreatic veins have fallen out of favor. The preoperative localization with ^{18}Fluoro-L-DOPA-PET-CT is currently acknowledged to be the most accurate investigation for distinguishing between focal and diffuse. Although this has become the standard for preoperative localization it still remains limited in its availability. With this in mind, the treating team and pediatric surgeon consultation must take this into consideration.

High case volume and experience are necessary to generate consistently good results and a very low complication rate. Laparoscopic techniques are clearly feasible in the treatment of patients with HI and will likely become standard for initial biopsy and diagnosis and for the resection of focal lesions. As we learn more about the genetics and molecular biology of congenital HI, we will soon have many more options for diagnosis, classification, and treatment, perhaps in some cases obviating the need for surgical intervention.

Suggested Reading

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