A Multidisciplinary Approach to the Focal Form of Congenital Hyperinsulinism Leads to Successful Treatment by Partial Pancreatectomy

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Background/Purpose: Congenital hyperinsulinism (HI) causes severe hypoglycemia in neonates and infants. Reccessive mutations of the beta-cell K\textsubscript{ATP} channel genes cause diffuse HI, whereas loss of heterozygosity together with inheritance of a paternal mutation cause focal adenomatous HI. Although these 2 forms of HI are clinically identical, focal HI can be cured surgically. The authors reviewed their experience with partial pancreatectomy for focal HI.

Methods: From December 1998 to January 2003, 38 patients (ages 2 weeks to 14 months; median age, 10 weeks) were treated with partial pancreatectomy for focal HI. Before surgery, patients had localization studies using selective arterial calcium stimulation with venous sampling or transhepatic portal venous sampling. At operation, the focal lesion was found using the preoperative localization data and multiple pancreatic biopsies with frozen section analysis, followed by partial pancreatectomy. A complete response at follow-up was defined as no requirement for glycemic medications, no continuous tube feedings, and no diabetes mellitus.

Results: Nineteen pancreatic focal lesions were in the head; 15 were in the neck, body, or tail; and 4 had more extensive involvement. Lesions that required substantial resection of the pancreatic head underwent Roux-en-Y pancreaticojejunostomy to preserve the normal body and tail. Lesions of the body or tail were usually treated with partial distal pancreatectomy. Ninety-two percent (35 of 38) of patients had a complete response to surgery. Three patients have required glycemic medications. No patient is diabetic. Surgical complications included additional resection for residual disease (3), small bowel obstruction requiring laparotomy and enteralysis (2), and chylous ascites (3) that resolved with medical management.

Conclusions: A multidisciplinary approach to patients with the focal form of congenital hyperinsulinism can distinguish focal from diffuse disease, localize focal lesions, and permit partial pancreatectomy with cure in most patients.

INDEX WORDS: Hyperinsulinism, hypoglycemia, pancreatectomy.

INAPPROPRIATE OVERSECRETION of insulin is the hallmark of congenital hyperinsulinism (HI). It is the most common cause of persistent hypoglycemia in neonates and can lead to irreversible brain damage.\textsuperscript{1} Recent studies have shown that abnormalities of the K\textsubscript{ATP} channel, which are encoded by the sulfonylurea receptor 1 (\textit{SUR1}) and \textit{Kir6.2} genes, are responsible for altered control of insulin secretion.\textsuperscript{2-4} In response to elevated glucose levels, the K\textsubscript{ATP} channel closes, depolarizing the \(\beta\)-cell membrane and initiating calcium-dependent release of insulin from the \(\beta\)-cell storage granules. Uncontrolled insulin secretion may occur if either the \textit{SUR1} or \textit{Kir6.2} proteins are defective.\textsuperscript{5} The \textit{SUR1}/\textit{Kir6.2} form of HI may not be controlled with medical therapy such as diazoxide, which acts on \textit{SUR1} to suppress insulin secretion, and pancreatectomy is often necessary. In contrast, surgery is not usually necessary in other genetic forms of HI that result from mutations of glucokinase or glutamate dehydrogenase genes that are responsive to diazoxide treatment.\textsuperscript{6}

Neonates with HI may have either diffuse involvement of the pancreatic \(\beta\)-cells or focal adenomatous islet cell hyperplasia. Mutations of the \textit{SUR1}/\textit{Kir6.2} complex appear to be involved in both of these types. Recessive mutations cause diffuse HI, whereas loss of heterozygosity together with inheritance of a paternal mutation cause focal adenomatous HI.\textsuperscript{7} These 2 forms of HI are clinically identical. Patients with diffuse disease often require near-total pancreatectomy, which has the long-term risk of diabetes mellitus.\textsuperscript{8} Conversely, babies with focal disease potentially can be cured with a selective partial pancreatectomy with little risk of subsequent diabetes.\textsuperscript{9} We reviewed our experience with a multidisciplinary approach (pediatric endocrinology, interventional radiol-
ogy, pathology, and surgery) to patients with the focal form of HI to distinguish focal from diffuse disease, localize focal lesions, and treat focal disease with partial pancreatectomy.

MATERIALS AND METHODS

Study Population

This retrospective review was approved by the Institutional Review Board at the Children’s Hospital of Philadelphia (CHOP), Protocol #2949. From December 1998 to January 2003, 38 patients were treated with partial pancreatectomy for focal HI at the Center for Hyperinsulinism at CHOP. Two additional HI patients were referred to our center after a focal lesion was not found during 95% pancreatectomy. They each underwent exploration, and the focal lesion in the residual pancreas was excised.

During this same 4-year period, there were 24 patients with diffuse HI who had intraoperative biopsies to confirm the diagnosis and then underwent near-total pancreatectomy. The diagnosis, treatment, and clinical outcome of these diffuse HI patients are not reviewed in this report.

Diagnosis and Medical Management by Pediatric Endocrinology

The diagnosis of congenital HI was established if fasting hypoglycemia (glucose <50 mg/dL) occurred simultaneously with an inappropriately elevated plasma insulin (>2.0 μU/mL), low plasma beta-hydroxybutyrate (<2.0 mmol/L) and free fatty acids (<1.5 mmol/L), and an inappropriate glycemic response to intravenous glucagon (>30 mg/dL rise in serum glucose level). Medical therapy to maintain euglycemia was standardized and involved high continuous intravenous infusions of glucose as measured by the Glucose Insulin Rate (which is the amount of glucose infused in milligrams per kilogram per minute), frequent oral feedings, and administration of diazoxide, glucagon, octreotide, and occasionally nifedipine. Before surgery, patients underwent acute insulin response (AIR) testing while on the pediatric endocrinology service to distinguish focal from diffuse HI. The technique and findings for AIR testing have been described previously by our group.10,11

Localization Procedures Performed by Interventional Radiology

The next step in the diagnostic evaluation was the Arterial Stimulation with Venous Sampling (ASVS) test. The technique of selective intraarterial injection of calcium gluconate to locate insulinomas in adult patients was first described by Doppman12 and has been modified to be applied in infants by our group.11 A catheter was positioned in the right hepatic vein using a right internal jugular vein approach. Blood samples for insulin levels were obtained through the hepatic vein catheter after selective injection of calcium into the arteries (gastroduodenal, superior mesenteric, and splenic arteries) that supply various regions of the pancreas. An immediate rise in insulin from stimulation in only 1 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 3 areas suggests diffuse HI. A few patients also underwent transhepatic portal venous catheterization (THPVS) and selective sampling of the pancreatic veins using the technique first described by Brunelle et al.13 Both techniques require that the patient be off all glycemic medications (5 days for diazoxide, 1 to 2 days for octreotide) before catheterization under general anesthesia. THPVS requires that glucose levels be maintained at 50 mg/dL during the procedure compared with 60 to 80 mg/dL for ASVS. For THPVS, the pancreatic venous insulin levels were compared with simultaneously drawn plasma levels of insulin and glucose.

Surgical Procedure and Histopathology

All operations were approached in a similar manner via a transverse supraumbilical laparotomy. The pancreas was exposed by an extended Kocher maneuver, entry into the lesser sac, and mobilization of the spleen and the inferior border of the pancreas. The pancreas was inspected under 3.5X loupe magnification in an attempt to visualize a focal lesion. If no focal lesion was seen, then 3- to 5-mm-diameter biopsy specimens were taken each from the pancreatic head, body, and tail. The specimens were placed in freezing embedding medium (Cryomatrix; Thermo Shandon, Pittsburgh, PA) and snap frozen. Cryostat sections were fixed in methanol and stained with H & E. When these random specimens showed normal pancreatic histology, a further search for the focal lesion using the preoperative localization data was conducted. Additional biopsy specimens of suspicious areas continued to be obtained until the focal lesion was diagnosed by frozen section.

The histologic criteria of Rahier et al14 were used for the diagnosis of the focal lesion. Briefly, a focal lesion is characterized by a tumorlike proliferation of islet cells that push exocrine elements aside or haphazardly incorporate them (Fig 1). Unlike insulinomas, the focal lesion retains the lobular architecture of the normal pancreas, and exocrine elements usually remain within the lesion. The lesions often have irregular borders, and the endocrine cells frequently have enlarged nuclei. Islets outside the lesion appear normal. Insulinomas also differ from focal lesions because they usually are straightforward to identify intraoperatively and occur in older children. Patients with diffuse disease have abnormal islets containing 5% to 10% of cells with enlarged nuclei present throughout the pancreas.15

Once the focal lesion was identified, a partial pancreatectomy was performed using frozen sections of margins to ensure a complete resection. For periductal lesions in the body and tail, a distal pancreatectomy was performed. Lesions that required substantial resection of the pancreatic head were reconstructed with Roux-en-Y pancreaticojejunostomy to preserve the normal body and tail. After the surgery, all frozen samples were processed for routine histology and confirmation of findings based on paraffin-embedded sections.

Postoperative Care and Follow-up

Postoperative management was standardized by a clinical care pathway including the use of the Glucose Infusion Rate to quantify the patient’s glucose requirement. After hospital discharge, a complete response at follow-up was defined as no requirement for glycemic medications, no continuous tube feedings, and no diabetes mellitus.

RESULTS

For the 38 patients with focal HI, there were 21 girls and 17 boys. The age at operation ranged from 13 days to 14 months with a median age of 10 weeks.

Nineteen focal lesions were in the pancreatic head; 15 were in the neck, body, or tail; and 4 had more extensive involvement. Although 27 lesions were 10 mm or less in diameter, 11 lesions were larger than 10 mm, and some were much larger than that size. Some lesions had octopuslike tentacles that made imperative the intraoperative confirmation of clear margins by frozen section analysis. Twelve patients had focal lesions that extended into the portion of the pancreatic head that is normally left after a 95% pancreatectomy (the region between the
common bile duct and the duodenal wall). Although focal lesions maintain a lobular structure similar to that of the normal pancreas, subtle visual clues (ranging from a slightly reddish-brown color to a marblelike appearance) permitted visual detection of the lesion intraoperatively by the surgeon in 24 of the 38 cases, including 18 of the last 23 cases. Accurate preoperative localization studies greatly facilitated the visual search for a focal lesion.

**Fig 1.** (A) Cut surface of pancreatectomy specimen through suspected focal lesion (marked by suture). (B) Chromogranin A immunolabelling highlights the architecture of the focal lesion (left) and adjacent normal pancreas (right). (C&D) Comparison of cytologic features of the endocrine tissue in the focal lesion (C) and normal pancreas (D). Note enlarged nuclei.
lesion. In some cases, the lesion felt firmer than the surrounding normal pancreas.

ASVS was performed in 36 patients (2 other patients had arteries that were too small for cannulation), and transhepatic catheterization of the portal and pancreatic veins was performed either instead of or in addition to ASVS in 6 others. The region of hypersecretion of insulin was identified by ASVS in a total of 26 of 36 (72%) cases, whereas transhepatic catheterization produced accurate localization data in only 2 of 6 (33%) of cases. Three patients had femoral arterial thrombosis after ASVS, which was treated successfully with either systemic anticoagulation or thrombolysis therapy.

Five patients with lesions that required substantial resection of the pancreatic head underwent Roux-en-Y pancreaticojejunostomy to preserve the normal pancreatic body and tail. Lesions of the body or tail that were near the main pancreatic duct were treated with a partial distal pancreatectomy. The extent of pancreatectomy ranged from 5% to 98%. Most patients (63%) underwent a pancreatectomy of 50% or less. Ninety-two percent (35 of 38) of patients had a complete response to surgery. Three patients have required glycemic medications. No patient is diabetic. There were no injuries to the common bile duct and no cases of duodenal necrosis, and the spleen was preserved in all cases. In 3 cases involving a lesion in the pancreatic head, the lesion was not completely resected, hypoglycemia persisted postoperatively, and another laparotomy was required for resection of residual disease with cure in 2 of the 3 patients. Other surgical complications included 3 cases of chylous ascites that resolved quickly with a change to an elemental formula and 2 cases of small bowel obstruction requiring laparotomy and lysis of adhesions.

For the 2 additional patients who were referred after 95% pancreatectomy performed elsewhere, the focal lesion was present in the residual pancreatic head tissue and the lesion was resected. One patient is an insulin-dependent diabetic and also requires pancreatic enzymes. The other patient has persistent hypoglycemia requiring medical therapy despite 2 operations leading to a complete pancreactectomy with choledochoduodenostomy; we suspect that there is additional unresected focal disease within the duodenal wall.

DISCUSSION

Congenital hyperinsulinism is a rare derangement of glucose metabolism, which carries an estimated incidence of 1 to 1.4 in 50,000 live births, leading to 80 to 120 new cases in the United States each year.\(^1\) Subtotal pancreatectomy for management of persistent infantile hypoglycemia was first performed at the Children’s Hospital of Philadelphia in 1950.\(^16\) In 1999, we reported a 35-year experience with subtotal (<95%) and near-total (95% to 98%) pancreatectomy in 53 patients with HI.\(^17\) We found that 21% of the patients had histologic evidence of a focal lesion in the pancreatectomy specimen. From December 1998 until January 2003, there were 64 pancreatectomies for HI performed at CHOP, and 40 (62.5%) of these cases proved to be focal disease suggesting that focal adenomatous islet cell hyperplasia is more frequent than previously appreciated. De Longlay-Debeney and the group from Paris described a method of transhepatic portal and pancreatic venous sampling of insulin to distinguish focal from diffuse HI.\(^13\) Differentiating between focal and diffuse disease with preoperative transhepatic portal venous sampling and intraoperative histologic techniques permitted limited pancreatectomy that was curative in patients with focal disease, and this approach prevented the development of postoperative diabetes.\(^18\)\(^,\)\(^19\)

We adopted the strategy promulgated by the Paris group, and modified it by developing 2 additional preoperative diagnostic methods in the infants—acute insulin response testing\(^10\)\(^,\)\(^11\) and an angiographic localization procedure using selective arterial calcium injection (ASVS). Since 1989, THPVS has been considered the best diagnostic technique because it can give precise information about focal lesion location. However, we now prefer ASVS for regional localization of a focal lesion, and this technique was successful in providing useful information about lesion location in 72% of our cases. Unlike ASVS, THPVS requires strictly controlled hypoglycemia to suppress insulin release from normal pancreas, is technically more difficult to perform, and mandates large-volume venous sampling that invariably leads to blood transfusion. In addition, THPVS is more technically challenging than ASVS because of the difficulty of catheterizing all of the small peripancreatic veins. Although ASVS only provides localization by pancreatic region, we have found that this is sufficient to guide the intraoperative search for the lesion by both loupe-enhanced visualization and analysis of frozen section biopsies. We also have learned that greater operative experience led to more frequent intraoperative visualization of the focal lesion.

We have tried other diagnostic radiology tests such as ultrasound scan (both preoperative and intraoperative), magnetic resonance imaging, computerized tomography, contrast angiography, radio-labelled octreotide scans, and positron emission tomography, but all have been unsuccessful in identifying these small lesions. For insulinoma localization in adults, intraoperative saline injection into the pancreas followed by tissue aspiration with rapid insulin measurements has been helpful,\(^20\) but we found that this localization technique was untenable in the fragile neonatal pancreas.

Because more than 50% of the focal lesions in this series involved the pancreatic head, conventional 95% pancreatectomy would have been inadequate therapy in many of these cases. The 2 patients who underwent 95%
pancreatectomy elsewhere with the focal lesion remaining within the residual pancreas, are good examples of this potential pitfall. With pancreatic head lesions close to the common bile duct or pancreatic duct, it can be tricky to excise all of the lesion, particularly if there are tentacles of diseased tissue that emanate from the lesion. To ensure complete lesion resection in these challenging cases, we now have a low threshold to remove most or all of the pancreatic head followed by Roux-en-Y pancreaticojejunostomy to drain the remaining pancreatic body and tail. Early in our experience, we were reluctant to use this approach in neonates and infants, but this led to inadequate resection in a few cases, which necessitated either another resection or continued medical therapy.

Patients with diffuse disease have recessively inherited mutations of the SUR1/Kir6.2 complex, whereas patients with focal disease have normal β-cells as well as a focal clone of abnormal β-cells that are homozygous for the SUR1/Kir6.2 mutation. The focal lesions arise by a 2-hit loss-of-heterozygosity mechanism. First, there is a specific loss of maternal alleles of the imprinted chromosome region 11p15 in cells from the focal lesion but not in the surrounding normal pancreatic cells. Second, there is a transmission of a mutation of SUR1/Kir6.2 in the paternal chromosome 11p; focal lesions have been linked to non-Mendelian expression of paternally transmitted SUR1 mutation in which there is duplication and reduction to homozygosity of the mutant paternal allele. In the future, molecular biology testing of peripheral leukocytes may help differentiate focal from diffuse disease. However, the search for mutations is currently of limited use in clinical practice because the process takes many weeks, and not all mutations are known.

We have learned that a multidisciplinary approach involving pediatric specialists in endocrinology, intervention radiology, pathology, and surgery can effectively diagnose and treat cases of congenital HI. A calcium angiogram can localize focal lesions within a specific region of the pancreas. Preoperative localization studies facilitate the intraoperative search for the focal lesion using loupe-magnification and frozen section analysis of pancreatic biopsies. Once the lesion is found, a partial pancreatectomy can be performed. This management strategy can help avoid the need for near-total pancreatectomy, which can miss a focal lesion in the pancreatic head and can lead to the ultimate development of diabetes mellitus. This study supports the importance of efforts to diagnose and localize focal lesions.

REFERENCES

Discussion

Unidentified Speaker: Scott, I was very impressed with this beautifully presented paper, and I have a question. The very difficult area of dissection there around the common bile duct, I wonder if you have any tips as to how one might accomplish that.

N.S. Adzick (response): One of the tricks that I learned actually from Professor Lewis Spitz is that one can put a vessel loop around the distal common bile duct and then swing that within the duodenal C-loop, and then one can trace the common duct right through the head of the pancreas.

P. Bagolan (Rome, Italy): Thank you, Dr Adzick. I enjoyed very much your paper. My question is, in your opinion, is there any place for laparoscopy in the diagnostic flow chart to do laparoscopy and multiple biopsies to distinguish between diffuse and focal before definitive surgery?

N.S. Adzick (response): We all know that folks are doing more and more things via laparoscopy, and it is conceivable that one could do this operation laparoscopically, but I think it would be extraordinarily difficult.

L. Spitz (London, England): It has taken many years to convince me of the existence of the focal form of the condition, but I am now converted. Our problem with pancreatic venous sampling is an accuracy rate of only 50% in localizing the focal area.

We have recently used laparoscopy to biopsy the tail of the pancreas, which is then submitted for histopathologic examination. If this shows diffuse disease, we will proceed to near-total pancreatectomy, and we would only perform pancreatic venous sampling if the biopsy showed focal disease.

N.S. Adzick (response): I think we will hear much more today from Professor Fekete when she reviews their experience in Paris.

J. O’Neill (Nashville, TN): During the time that you encountered these focal lesions, how many diffuse lesions were there? Because this would tell us a little bit about the incidence at least over this 4-year period.

N.S. Adzick (response): During that same 4 years, there were 24 patients who had diffuse disease who underwent near-total pancreatectomy, and there were 2 referrals of patients who had focal disease who had had a 95% pancreatectomy done elsewhere and still had the focal lesion in the remnant in the pancreatic head, so that brings the total number of patients during 4 years to 64.