Laparoscopic Diagnosis and Cure of Hyperinsulinism in Two Cases of Focal Adenomatous Hyperplasia in Infancy

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ABSTRACT. Persistent hyperinsulinemic hypoglycemia of infancy or congenital hyperinsulinism of the neonate is a rare condition that may cause severe neurologic damage if the disease is unrecognized or inadequately treated. Current treatment aims to restore normal blood glucose levels by providing a carbohydrate-enriched diet and drugs that inhibit insulin secretion. If medical treatment fails, then surgery is required. Because congenital hyperinsulinism may be caused either by diffuse involvement of pancreatic β-cells or by a focal cluster of abnormal β-cells, the extent of pancreatectomy varies. We report on 2 patients with a focal form of the disease for whom diagnosis was made with laparoscopy. Laparoscopic enucleation of the lesion was curative. Pediatrics 2004;114:520–522. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2003-1180-L; congenital hyperinsulinism, pancreatectomy, laparoscopy, neurodevelopmental outcome.

ABBREVIATIONS. PHHI, persistent hyperinsulinemic hypoglycemia of infancy; PVS, pancreatic venous sampling; K<sub>ATP</sub> channel, adenine triphosphate-sensitive potassium channel; SUR, sulfonylurea receptor; Kir, potassium inward rectifier.

Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), or congenital hyperinsulinism, is a rare disease characterized by inappropriate insulin secretion in the presence of hypoglycemia. Severe neurodevelopmental morbidity among these patients is reportedly attributable to late diagnosis and/or inability to control the profound hypoglycemia. Most cases are attributable to mutations in the genes coding for the subunits of the adenose triphosphate-sensitive potassium (K<sub>ATP</sub>) channels in pancreatic β-cells, sulfonylurea receptor (SUR)1 (ABCC8) and potassium inward rectifier (Kir)6.2 (KCNJ11).1 In rarer cases of PHHI, mutations in the glucokinase gene (GCK), glutamate dehydrogenase gene (GLUD1), and short-chain hydroxacyl-coenzyme A dehydrogenase gene (HADHSC) gene are pathogenic and act mainly by subverting the operation of K<sub>ATP</sub> channels.2,3 Treatment is directed to ward normoglycemia, through provision of adequate carbohydrate coverage and the use of drugs that interact with the ion channels to lower insulin secretion.4 Diazoxide, octreotide, and calcium channel blockers are available, but diazoxide is the drug of choice. PHHI is a heterogeneous disease; in a few cases, it may be transient and mild, requiring only short-term medical treatment. In other cases, including those involving mutations in glucokinase, glutamate dehydrogenase, and short-chain hydroxacyl-coenzyme A dehydrogenase genes, diazoxide and appropriate diet are required for a longer time but are very effective in controlling hypoglycemia.2,5,6 However, almost 80% of neonates with congenital hyperinsulinism fail to respond to medical treatment and require near-total pancreatectomy.5 This procedure leads to important digestive and endocrine morbidities, whereas removal of insufficient amounts of the pancreas increases the duration of hypoglycemia, necessitates reintervention, and enhances the risk of hypoglycemic neuronal injury.

The observations in 19757 and then in 19898 that PHHI may be caused by either diffuse or focal abnormalities of β-cells changed the surgical approach and led to the development of radiologic procedures to identify these focal forms. We now report on 2 children with PHHI for whom a focal lesion was diagnosed during laparoscopy and for whom laparoscopic enucleation was curative.

CASE REPORTS

Patient 1

Patient 1 is the third child of healthy unrelated parents. He was born after an uneventful pregnancy, with a birth weight of 3980 g. During the first day of life, he became cyanotic and lethargic and was admitted to the hospital. The blood glucose level was 10.8 mg/dL (0.6 mmol/L). Glucose was administered intravenously, and evaluation for hypoglycemia was performed. The diagnosis of PHHI was established quickly because of several high serum insulin measurements in the presence of blood sugar levels of <36 mg/dL (<<2 mmol/L). Pancreatic sonographic findings were normal. Frequent carbohydrate feedings were administered, and high concentrations of glucose were infused intravenously through a central catheter. Diazoxide (10 mg/kg) and hydrochlorothiazide (2 mg/kg) administration was initiated, but asymptomatic hypoglycemia persisted. Nifedipine (1.1 mg/kg) and octreotide (up to 10 μg/kg) were added. Ocreotide administration was soon discontinued because of ileus. The patient’s weight increased to 5.5 kg at 1 month of age, and the glucose requirement was increased to 31 mg/kg per minute. At the age of 31 days, a diagnostic laparoscopy was performed. After mobilization of the lower border of the pancreas, a small round lesion of 5-mm diameter was observed close to the incisura pancreatis. The lesion was excised. After laparoscopy, blood glucose levels remained stable, medication was discontinued, and the patient was discharged with nor-
mal bottle feeding. At the age of 13 months, his glucose metabolism is still normal and his neurologic development is excellent.

The histologic examination revealed a rich proliferation of islet cells, most of which stained positive for insulin. Cultured islet cells were prepared with standard methods, and patch-clamp experiments were undertaken to show that K\textsubscript{ATP} channels in PHHI \(\beta\)-cells were defective and there were no functional responses to diazoxide. DNA analysis of peripheral blood lymphocytes revealed a heterozygous mutation in SURI gene exon 12 (1792C\(\rightarrow\)T, resulting in the amino acid substitution R598X), which was also found for the father.

Patient 2

Patient 2 is the third child of unrelated parents. She was born after an uneventful pregnancy, with a birth weight of 3700 g. During the first day of life, she became irritable and subsequently lethargic and was admitted to the hospital, where a blood glucose level of 18 mg/dL (1.0 mmol/L) was measured. Despite glucose administration, new episodes of hypoglycemia occurred, followed by seizures. The finding of inappropriately high serum insulin levels in the presence of hypoglycemia established the diagnosis of PHHI. Intravenous glucose administration and frequent feedings were necessary, bringing the glucose requirement to 16 mg/kg per minute. Diazoxide, hydrochlorothiazide, and nifedipine were administered, without improvement of glucose levels. Sonographic findings for the pancreas were normal. On day 29, diagnostic laparoscopy was performed. A lesion in the head of the pancreas (6 mm \(\times\) 5 mm) was identified and enucleated. Except for transient hyperglycemia, the patient was well after discontinuation of all medication and was fed with a normal infant feeding regimen. At the age of 12 months, glucose metabolism is still normal and the child is developing normally.

The histologic examination of the lesion showed adenomatous cell proliferation of predominantly insulin-staining islet cells. Electrophysiologic studies of the cultured islets revealed defects in the electrical activity of K\textsubscript{ATP} channels. DNA analysis of peripheral blood lymphocytes revealed a heterozygous mutation in exon 3 of the SURI gene (331G\(\rightarrow\)A, resulting in the amino acid substitution G111R), which was also found for the father.

DISCUSSION

We report on 2 infants with PHHI for whom focal lesions of the pancreas were diagnosed during laparoscopy and laparoscopically enucleated. Both children were cured at the age of 1 month. One year after surgery, both patients are well and normoglycemic. Functional data from patient tissue analyses and genotyping in both cases revealed that PHHI was a consequence of defects in \(\beta\)-cell K\textsubscript{ATP} channels. For both children, mutations in the SURI gene were found; the mutations were of paternal origin in both cases, as reported for focal hyperinsulinism. The focal origins of PHHI were confirmed with histologic diagnoses.

Focal adenomatous hyperplasia as a cause of PHHI was observed first by Kloppel et al\(^7\) in 1975 and was noted by Goossens et al\(^6\) in 1989 in a large study of 24 pancreata from surgically treated patients with PHHI. Since those observations, focal lesions as a cause of intractable hyperinsulinism have been consistently reported. The presumed incidence may be as high as 30% to 60% of cases of congenital hyperinsulinism.\(^6,9,10\) Diffuse hyperinsulinism and focal hyperinsulinism have the same clinical presentations but differ in their genetic origins and treatment. Diffuse congenital hyperinsulinism is predominantly an autosomal recessive disease, arising from homozygous mutations in the Kir6.2 or SURI genes. Focal forms of congenital hyperinsulinism result from a paternally inherited Kir6.2 or SURI mutation and loss of maternal 11p15 material in the lesion.\(^11\) Because limited pancreatectomy is potentially curative for focal lesions, techniques were developed that might help identify these focal pancreatic lesions. Unfortunately, standard radiologic techniques, such as ultrasonography, computed tomography, and magnetic resonance imaging, are not helpful. In 1989, French interventional radiologists and surgeons developed the technique of pancreatic venous sampling (PVS), using percutaneous transhepatic catheterization of the portal vein.\(^10,12\) In these diagnostic studies, the distinction between focal and diffuse hyperinsulinism is made on the basis of the finding of high insulin levels in venous blood collected from a single pancreatic area, as opposed to high insulin levels in all pancreatic veins. An alternative method involves the calcium infusion test, whereby calcium is selectively infused in the gastroduodenal, superior mesenteric, and splenic arteries and hepatic venous blood is sampled for insulin measurements.\(^13\) Both procedures require intensive radiologic investigation, radiation, and anesthesia. PVS seems to be the most accurate method\(^13\) but has proved to be difficult to implement in most pediatric centers.\(^14\) Recently, Otonkoski et al\(^15\) presented preliminary data suggesting the usefulness of positron emission tomography with \(\text{[18F]}\text{fluoro-L-dopa}\) for localization of focal lesions.

Laparoscopy is a new diagnostic approach for the identification of focal lesions. The technical aspects were discussed previously.\(^16\) The combination of magnification (up to 18-fold when the 5-mm scope is at a distance from the object of 2 cm) and the “palpation” of the pancreatic tissue with a suction cannula allows identification of lesions in the entire pancreas. After detachment of the lower border of the pancreas, the posterior part of the pancreas can also be well visualized and searched with a palpating probe. The focal lesions are variable in size, ranging from microscopic lesions (measuring <10 mm\(^7\)) to lesions that are visible with the naked eye or magnifying loupes with 3.5-fold enlargement.\(^12\) The lower limit of detection of lesions with laparoscopy is not known, and it is logical to assume that microscopic lesions may be missed. However, such lesions may also remain undetected with PVS, which has success rates of 71% to 89%.\(^10,12\) Another potential problem is the presence of multiple small lesions. However, multifocality appears to be unusual,\(^17\) with multiple nodules being 5 times less frequent than single lesions.\(^18\) Finally, complete visualization of the pancreas and identification of lesion(s) should prevent the unfortunate situation of persisting hypoglycemia after blind, near-total pancreatectomy, with 1 or more lesions being left in the pancreatic remnant.\(^14,19\) The laparoscopic approach offers other advantages. This procedure is safe and quick, and serum glucose levels can be maintained within a safe range during the procedure with the continuation of medical treatment. This is a major advantage in comparison with the continuous PVS technique, which requires medical treatment to be stopped for 5 days and blood glucose levels to be maintained between 36 mg/dL (2 mmol/L) and 54 mg/dL (3 mmol/L) during the sampling procedure.\(^10\) Also, no radiation is involved in our approach and no insertion of catheters into the main vessels or arteriography is necessary.
Laparoscopic exploration can be performed at any age, whereas PVS is generally not performed before age 30 days.

The recognition by pathologists of focal lesions has changed the current treatment approach for patients with PHHI. For patients with diffuse hyperinsulinism, a near-total pancreatectomy is required to control hypoglycemia, whereas elective partial pancreatectomy is sufficient for the treatment of patients with focal disease, which eliminates the risk of significant morbidity for a large number of patients. Indeed, de Lonlay-Debeney et al. reported normal or near-total pancreatectomy in 14, 19, 20 and exocrine pancreatic insufficiency in 20% of cases. Laparoscopic enucleation of a focal lesion has been reported previously, whereas laparoscopic subtotal pancreatectomy for treatment of PHHI was reported once. In both of our cases, identification and removal of the lesion were easy and did not cause complications. Moreover, the cosmetic results were excellent, with the scars being barely visible. Both patients had a single lesion. In addition to careful palpation, we could have considered the approach reported by Craver and Hill to rule out the presence of multiple lesions. In their experience, the finding of sustained normal serum glucose levels after enucleation of a focal lesion and discontinuation of the glucose infusions argues against the presence of hidden focal lesions.

In our cases, 1-year follow-up assessments revealed no recurrence of hypoglycemia. We are convinced that early laparoscopy for infants with congenital hyperinsulinism may substantially improve outcomes. Presently, the reported outcomes for children with PHHI are unfavorable. In addition to the aforementioned increased incidences of diabetes mellitus and exocrine pancreatic insufficiency related to subtotal pancreatectomy, up to 50% of patients with PHHI experience psychomotor or mental retardation. Reasons include poor or delayed diagnosis of the condition or delayed surgery. Early surgery (<100 days of age) is generally associated with improved neurodevelopmental outcomes and fewer endocrine and exocrine disturbances.

The 2 patients described in this article are the first and only patients at our institution who underwent laparoscopic exploration for PHHI. Although our experience is limited, our observations show that laparoscopic investigation is worthwhile and feasible for any patient with PHHI for whom medical treatment is insufficient to control insulin secretion. If a focal lesion is identified, then removal may be curative. If laparoscopy does not reveal a focal lesion, then multiple biopsies must be obtained during surgery, to determine peroperatively the diagnosis of diffuse versus focal hyperinsulinism. If pathologic examination results for the biopsies are inconclusive during the operation, then the procedure should be aborted. Reexploration should be conducted after definitive results have become available. The contribution of laparoscopy to both diagnosis and treatment will require additional evaluation, but the technique is likely to be highly valuable for the early diagnosis and cure of PHHI and improvement of the long-term outcomes for hyperinsulinism in infancy.

REFERENCES

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