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Management of postgastric bypass noninsulinoma pancreatogenous hypoglycemia

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Abstract
Introduction Postgastric bypass noninsulinoma hyperinsulinemic pancreatogenous hypoglycemia defines a group of patients with postprandial neuroglycopenic symptoms similar to insulinoma but in many cases more severe. There are few reports of patients with this condition. We describe our surgical experience for the management of this rare condition.
Methods A retrospective study was performed at St. Vincent Hospital, Indianapolis. Fifteen patients were identified with symptomatic postgastric bypass hypoglycemia for the period 2004–2008. All patients were initially treated with medical therapy for hypoglycemia. Nine patients eventually underwent surgical treatment. The preoperative workup included triple-phase contrast CT scan of the abdomen, endoscopic ultrasound of the pancreas, a 72-h fast followed by a mixed meal test, and calcium-stimulated selective arteriography. Intraoperative pancreatic ultrasound also was performed in all patients. Patients then underwent thorough abdominal exploration, exploration of the entire pancreas, and extended distal pancreatectomy.
Results Nine patients underwent surgery. The mean duration of symptoms was 14 months. The 72-h fast was negative in eight patients (as expected). Triple-phase contrast CT scan of the abdomen was negative in eight patients and showed a cyst in the head of pancreas in one patient. Extended distal (80%) pancreatectomy was performed in all nine patients. The procedure was attempted laparoscopically in eight patients but was converted to open in three. One patient had an open procedure from start to finish. Pathology showed changes compatible with nesidioblastosis with varying degrees of hyperplasia of islets and islet cells. Follow-up ranged from 8–54 (median, 22) months. All patients initially reported marked relief of symptoms. Over time, two patients had complete resolution of symptoms; three patients developed occasional symptoms (once or twice per month), which did not require any medication; two patients developed more frequent symptoms (more than twice per month), which were controlled with medications; and two patients had severe symptoms refractory to medical therapy (calcium channel blockers, diazoxide, octreotide).
Discussion Postprandial hypoglycemia after gastric bypass surgery with endogenous hyperinsulinemia is being increasingly recognized and reported in the literature. Our experience with nine patients is one of the largest. The etiology of this condition is not entirely understood. There may be yet unknown factors involved but increased secretion of glucagon-like peptide 1 and decreased grehlin are being implicated in islet cell hypertrophy. There is no "gold standard" treatment—medical or surgical—but distal pancreatectomy to debulk the hypertrophic islets and islet cells is the main surgical modality in patients with severe symptoms refractory to medical management.

Keywords Islet cell hyperplasia · Nesidioblastosis · Postgastric bypass · Noninsulinoma pancreatogenous hypoglycemia

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Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) describes a constellation of postprandial neuroglycopenic symptoms similar to insulinoma but in many cases more severe [1, 2]. Symptoms include confusion, disorientation, unconsciousness, syncope, shakiness, tremors, abnormal behavior, anxiety, weakness, blurred vision, and seizures [1, 2]. It is distinguished from insulinoma in that the symptoms occur after eating rather than in the fasting state. This syndrome was first and most completely described by investigators at the Mayo Clinic in 1999 and 2000 and appeared to be the result of nesidioblastosis, a type of islet cell hyperplasia of the pancreas [1–3]. Recommended treatment was 80% distal pancreatectomy. Several years later, in 2005, these investigators were the first to present a series of patients who were post-Roux-en-Y gastric bypass for morbid obesity [4]. There are few other case reports of this condition [5, 6]. The etiology of the hypoglycemia and the nesidioblastosis was unclear as was the association between the two. In other words, the morphology (nesidioblastosis) did not appear to correlate with the physiology (hypoglycemia). Gut hormones (incretins), such as glucagon-like-peptide 1 (GLP-1) and grehlin, may play a role in the disease process, but that role has not been elucidated [7–11]. This appears to be a rare condition as the number of cases reported is low compared with the number of gastric bypass procedures performed per year in the United States [4–6, 12, 13].

The first line of treatment is medical but operation in the form of distal or subtotal pancreatectomy is the primary surgical therapy in medically refractory patients. In this report, we describe our experience with the surgical management of this condition.

Materials and methods

Subjects

A retrospective study was performed at St Vincent Hospital, Indianapolis. Fifteen patients were referred with symptomatic postgastric bypass hypoglycemia for the period 2004–2008. All patients were initially treated with medical therapy for hypoglycemia, which included calcium channel blockers, diazoxide, and octreotide. The patients were started on Verapamil sustained release 100 mg orally daily. If patients had side effects or failed to respond, Diazoxide was added. The initial dose was 25 mg orally three times per day. The dose could be gradually increased up to 75 mg three times per day. Diazoxide and verapamil were used alone or in combination. If the patients failed to respond to the above two medications, Octreotide was added. The dose ranged from 25 μg subcutaneously daily to 50 μg subcutaneously three times per day. The patients were treated with medical therapy as long as they responded to it. Nine refractory patients eventually underwent surgical treatment.

Preoperative evaluation

All patients were extensively evaluated. Each patient underwent 72-h fast in the hospital as per Mayo Clinic protocol [4]. During this test, they were kept NPO and glucose, insulin, C-peptide, and proinsulin levels were checked every 6 h. They were checked more frequently after the glucose level decreased to <60 mg/dl. The test was complete if 72 h elapsed, patients had neuroglycopenic symptoms or plasma glucose decreased to <45 mg/dl (Fig. 1). After this test, a 5-h glucose tolerance test was performed. Initially, baseline insulin, glucose, and C-peptide levels were checked. Then, a mixed meal containing 50 g of carbohydrate was consumed over 30 min. Hourly insulin, glucose, and C-peptide levels were recorded.

A triple-phase CT scan of the abdomen with islet cell protocol was performed in all patients. Endoscopic ultrasound of the pancreas also was performed to rule out insulinoma.

All patients underwent calcium-stimulated selective mesenteric angiography. In this test, the arteries supplying the pancreas—the splenic, gastroduodenal, superior mesenteric, and hepatic arteries, are selectively cannulated and injected with calcium gluconate (0.025 mEq/kg body weight). After injection, insulin is measured in samples taken from the right hepatic vein before injection of calcium and 30, 60, 90, 120, and 180 s after injection of each artery (Figs. 2, 3).

Historically, this test has been done to narrow down the location of an insulinoma in the pancreas. In NIPHS, the theoretic use of the test is to determine where the bulk of disease is to guide the amount of pancreatic resection [4]. Generalizations are made about the pattern of disease based on the increase in insulin after injection of any particular artery. The body and tail of the pancreas are within the splenic artery distribution. The head and uncinate process are within the gastroduodenal artery distribution. The uncinate process and secondarily the head are within the distribution of the superior mesenteric artery. However, in our practice, an 80% pancreatectomy is performed in all patients. Therefore, the purpose of the test, in our hands, is to confirm the diagnosis, rather than guide extent of resection.

Surgical treatment

Each patient underwent surgical exploration. Intraoperative pancreatic ultrasound was performed to rule out insulinoma. The entire pancreas was explored. For the purpose

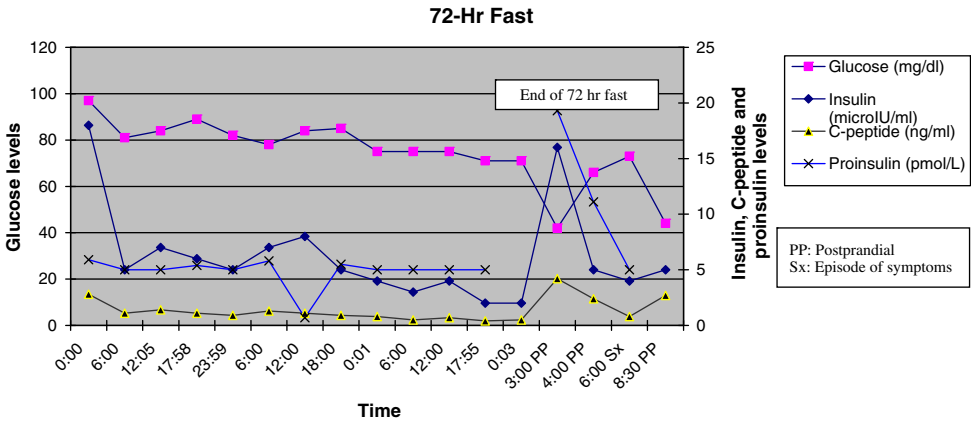

Fig. 1 72-h fast followed by mixed meal study. *PP* postprandial; *Sx* episode of symptoms

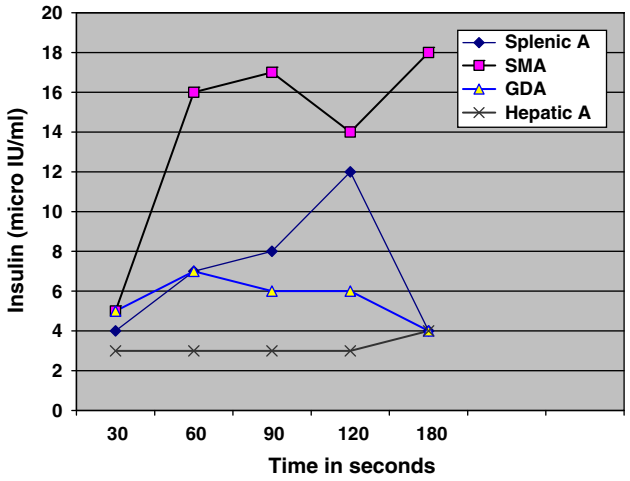

Fig. 2 Calcium-stimulated arteriogram showing increased insulin from both splenic artery and SMA distribution

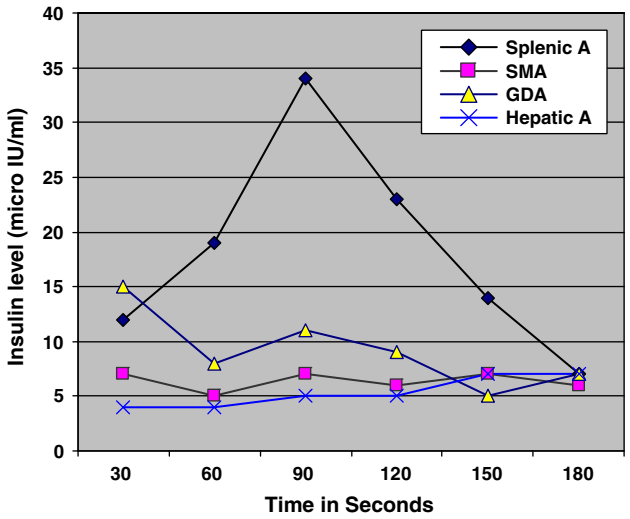

Fig. 3 Calcium-stimulated arteriogram showing insulin release mainly from splenic artery distribution

of this study, if the pancreas was transected to the left side of the portal vein, it was considered a distal pancreatectomy. If it was transected to the right side of portal vein, it was considered an extended distal (80%) pancreatectomy. Finally, if a small rim of tissue (1–2 cm) was left close to the duodenum and common bile duct, it was considered a near total pancreatectomy (95%). The pancreas was transected with a stapling device. A closed suction drain was placed (Figs. 4, 5).

Pathologic analysis

Our pathologists use the Mayo Clinic criteria for the diagnosis of nesidioblastosis [4]. That includes the following morphologic features: (1) hypertrophy of islets, (2) hypertrophy of beta cells within the islets, (3) islet cell "budding" from the ducts, (4) ductoinsular complexes, (5) scattered clusters of endocrine cells within the pancreatic parenchyma (Figs. 6, 7, 8). Immunohistochemical staining for insulin was performed to identify specific cells and rule out insulinoma (Fig. 9). To confirm the diagnosis, specimens were sent to the Mayo Clinic for review.

Statistical analysis

The results are given as mean or median with range.

Results

Clinical data

Nine patients underwent surgery (8 women; Table 1). The age range was 28–62 (median, 33) years. The onset of symptoms ranged from 1 month after Roux-en-Y gastric bypass to 56 months. The mean duration of symptoms was 14 months. Six patients had type 2 diabetes before gastric

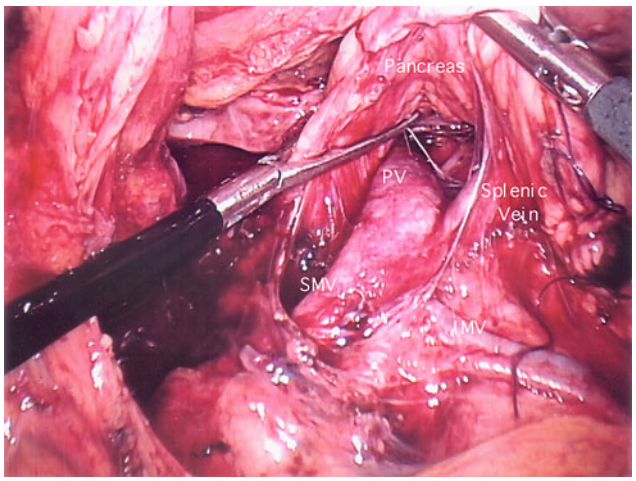

Fig. 4 Various structures identified during dissection

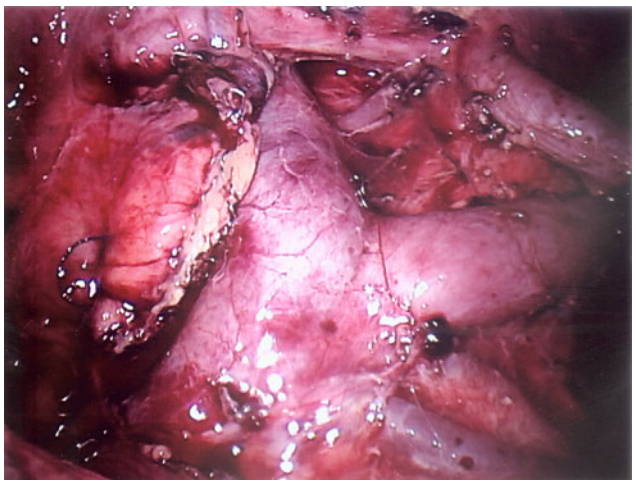

Fig. 5 The pancreas is transected to the right of the portal vein. This figure shows the structures as seen after extended distal pancreatectomy

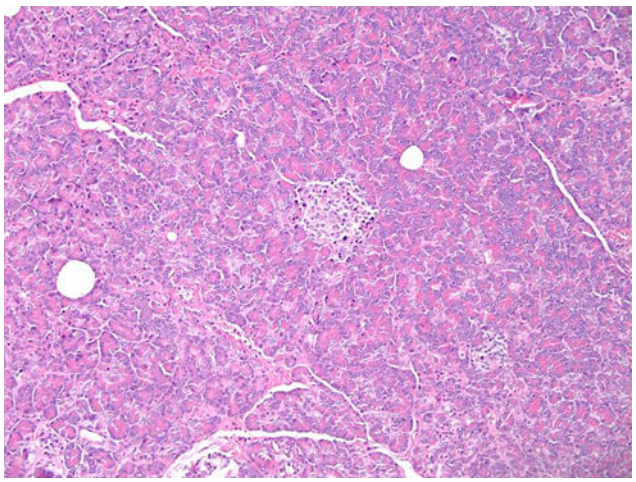

Fig. 6 Normal pancreas. H&E staining at 100× magnification

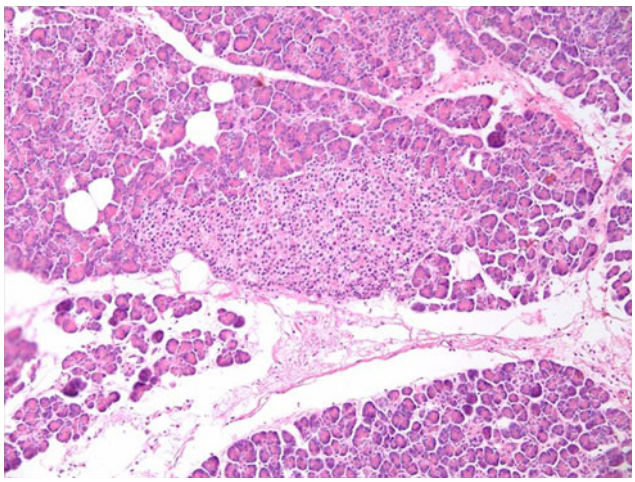

Fig. 7 Islet cell hypertrophy. H&E staining at 100× magnification

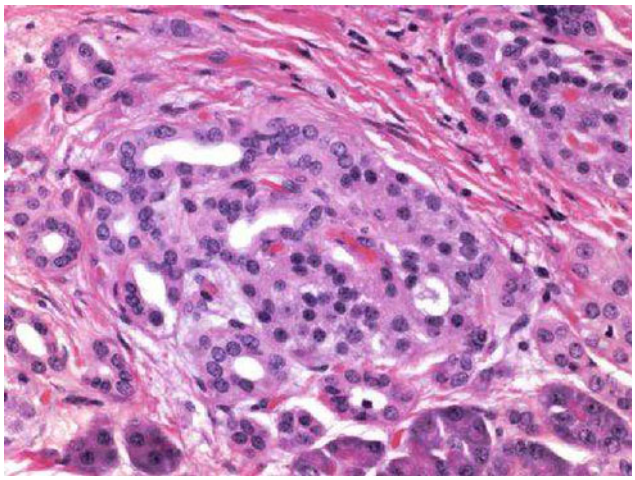

Fig. 8 Ductoinsular complex

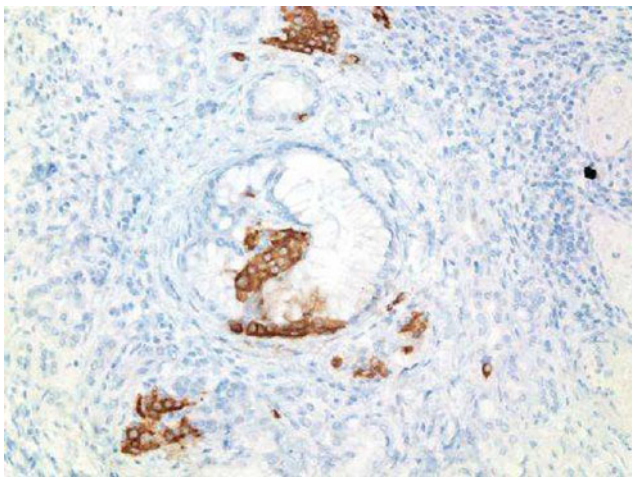

Fig. 9 Immunohistochemical staining for insulin showing ductoinsular complex

bypass, which resolved after their bariatric surgery. None of the patients had diabetes at the time of our evaluation. Symptoms were those of severe postprandial neuroglycopenia and included confusion, disorientation, unconsciousness, syncope, shakiness, weakness, blurred vision, tremors, and anxiety. The 72-h fast test was negative in eight patients (as expected). One patient had a positive test with both symptoms and plasma glucose <45 mg/dl at 42 h into the test. This patient had a history of chronic renal failure. A 5-h glucose tolerance test with mixed carbohydrate meal elicited varying degrees of postprandial hyperinsulinemia. Figure 1 shows a typical 72-h fast followed by mixed meal study. Patients did not develop typical neuroglycopenic symptoms with this test. We did offer reversal of gastric bypass to all patients, but none of the patients agreed.

A triple-phase contrast CT scan of the abdomen was negative in eight patients and showed a cyst in the head of pancreas in one patient. Endoscopic ultrasound confirmed a 1-cm cystic lesion in the head of pancreas in that patient. The final pathology of that lesion was mucinous cystadenoma, which was present in addition to islet cell hyperplasia. One more patient was found to have a small lesion in the tail of the pancreas on endoscopic ultrasound (final pathology showed 4-mm neuroendocrine tumor, which was negative for insulin).

Calcium-stimulated arteriography showed elevated insulin secretion with injection of the splenic and gastroduodenal arteries. Figure 2 shows increased insulin in two arterial distribution, and Fig. 3 shows increased insulin from one arterial distribution only. Some patients showed elevated insulin with stimulation of the superior mesenteric artery, in addition to the above, indicating a more diffuse involvement of the pancreas (Table 2).

Surgery

Extended distal (80%) pancreatectomy was performed in all nine patients (Figs. 4, 5). The spleen was spared in seven patients. The procedure was attempted laparoscopically in eight patients but was converted to open in three. One patient had an open procedure entirely. Three patients had a pancreatic leak, which was managed with a drain.

Pathology in all patients showed diffuse islet and islet cell hyperplasia with significant variability in size, shape, focal beta cell nuclear hypertrophy, and occasional ductoinsular complexes consistent with nesidioblastosis in all patients (Figs. 6, 7, 8, 9). In addition, one patient had 1-cm mucinous cystadenoma in the head of pancreas. Another patient was found to have a 4-mm neuroendocrine tumor; it was positive for chromogranin and synaptophysin but negative for insulin on histochemical staining. No insulinoma was identified in any patient (Table 3). The specimens for seven patients were sent to Mayo Clinic for pathological review for confirmation of the diagnosis.

Follow-up

Follow-up ranged from 8–54 (median, 22) months. All patients initially reported marked relief of symptoms. Over time, two patients had complete resolution of symptoms; three patients developed occasional symptoms (once or twice per month), which did not require any medication; two patients developed more frequent symptoms (more than twice per month), which were controlled with medications; and two patients had severe symptoms refractory to medical therapy (calcium channel blockers, diazoxide, octreotide). The first patient with severe symptoms underwent repeat preoperative workup and subsequently underwent near total (95%) pancreatectomy with marked, but not complete, improvement of symptoms. The second patient with severe symptoms also underwent near total pancreatectomy (95%). He has no symptoms during his short follow-up of 4 months so far. Two patients developed diabetes during follow-up, which required insulin therapy.

Table 1 Patient characteristics

Patient	Age (yr)	Gender (female or male)	Onset of hypoglycemia after gastric bypass (mo)	Duration of symptoms (mo)	Lowest glucose (mg/dl)	72-h fast
1	32	F	18	12	49	Negative
2	62	F	48	6	48	Positive
3	28	F	9	18	45	Negative
4	33	F	19	20	44	Negative
5	42	M	1	24	45	Negative
6	34	F	56	12	40	Negative
7	49	F	4	18	45	Negative
8	33	F	15	10	39	Negative
9	33	F	17	9	35	Negative

Table 2 Results of selective arterial calcium stimulation test

Patient	Baseline level of insulin from hepatic vein (micro IU/ml)	Splenic A[a] injection (micro IU/ml)	GDA[a] injection (micro IU/ml)	SMA[a] injection (micro IU/ml)	HA[a] injection (micro IU/ml)
1	4	34	11	7	5
2	2	16	10	4	3
3	4	26	17	11	4
4	4	12	19	20	4
5	4	15	36	4	4
6	3	8	4	9	3
7	4	52	39	23	6
8	3	12	6	17	3
9	4	67	122	8	8

GDA gastroduodenal artery; *SMA* superior mesenteric artery; *HA* hepatic artery

[a] Levels are drawn from the hepatic vein 60 s after selective arterial stimulation

Table 3 Operative procedure, pathology, and follow-up

Patient	Operation	Pathology	Complications	Postoperative medications	Symptoms	Follow-up (mo)
1	Lap extended distal pancreatectomy with splenic preservation	Nesidioblastosis	Pancreatic leak	None	None	8
2	Lap extended distal pancreatectomy with splenic preservation	Nesidioblastosis, 4-mm neuroendocrine tumor but no insulinoma	Diabetes	None	None	12
3	Lap extended distal pancreatectomy with splenic preservation	Nesidioblastosis	None	Yes	Mild hypoglycemia during menstruation	20
4	Lap extended distal pancreatectomy with splenic preservation	Nesidioblastosis	Pancreatic leak	No	Occasional symptoms with blood sugar in 50–60 s	13
5	Lap converted to open subtotal pancreatecto my with splenectomy	Nesidioblastosis	None	Yes	Erratic blood sugar between 40–300	26
	Required near total pancreatectomy 21 months after first surgery	Nesidioblastosis	None	None	None	4
6	Lap converted to open extended distal pancreatectomy and splenectomy	Nesidioblastosis	None	Yes	Occasional episodes of hypoglycemia with blood sugar in 50 s	36
7	Lap converted to open extended distal pancreatectomy with splenic preservation	Nesidioblastosis, 1 cm mucinous cystadenoma	None	No	Rare symptoms with blood sugar in 50–60 s	48
8	Lap extended distal pancreatectomy with splenic preservation	Nesidioblastosis	None	No	Rare symptoms with blood sugar in 60 s	22
9	Open extended distal pancreatectomy	Nesidioblastosis	Pancreatic Leak	Yes	Recurrent symptoms 18 months after first surgery	54
	Required near total pancreatectomy 2 years after first operation	Nesidioblastosis	Diabetes	No	Rare symptoms	30

Discussion

In a discussion of noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), it is essential to define terms, particularly because of the complexity and rarity of this disease. That will be done here along with a historical review of the subject.

The term nesidioblastosis was first coined by Laidlaw in 1938 and literally means "islet builder" [14]. He postulated that pancreatic ductal epithelial cells differentiated into islet cells, which then coalesced into hypertrophic islets.

In the ensuing years, nesidioblastosis became synonymous with persistent hyperinsulinemic hypoglycemia of infancy, which pediatric surgeons treated with near total pancreatectomy [15].

Sandler, in 1975, was the first to describe nesidioblastosis in an adult [16], and in 1981 Harness et al. described the first large series in adults: six patients treated with pancreatic resection that ranged from 50 to 100% with variable, but mostly satisfactory, relief of hypoglycemic symptoms [17].

The syndrome, its workup, and treatment were most completely described by Service et al. in 1999 and by Thompson et al. in 2000, both from the Mayo Clinic [1, 2]. They suggested the name noninsulinoma pancreatogenous hypoglycemic syndrome (NIPHS) as the most accurate description of the disease. Recommended treatment was 80% pancreatectomy. The same group of investigators was the first to report this entity in six patients who were postgastric bypass for morbid obesity [4].

In adults, insulinoma is the most common cause of persistent hyperinsulinemic hypoglycemia [18]. It is defined by Whipple's triad: symptoms provoked by fasting, blood glucose <50 mg/dl, and relief of symptoms with administration of glucose. In contrast, NIPHS is defined by (1) postprandial neuroglycopenic episodes, (2) documented hypoglycemia at the time of symptoms, (3) a negative 72-h fast, (4) negative preoperative imaging studies, and (5) a positive arterial calcium stimulation test.

The histologic criteria for nesidioblastosis are listed in Materials and methods. Others describe similar criteria—major criteria: (1) exclusion of an insulinoma by macroscopic, microscopic, and immunohistochemical examination; (2) multiple beta-cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm; (3) islets with normal spatial distribution of the various cell types; and (4) no proliferative activity of endocrine cells, and minor criteria: (1) irregular shape and occasional enlargement of islets; (2) increased number of islets; (3) lobulated islet structure; and (4) macro nucleoli in beta-cells [3].

There are only a few reports in the literature describing pancreatectomy for patients with postgastric bypass NIPHS. All patients reported had pathologic changes consistent with nesidioblastosis. Service et al., in their series of six patients, indicated that during a median period of 20 months, three patients were free of any postprandial symptoms, two patients had occasional mild symptoms, and one patient had more severe symptoms [4].

Patti et al. described three patients with postgastric bypass hypoglycemia [5]. In one patient, reversal of the gastric bypass was ineffective in reversing hypoglycemia. All three patients underwent partial pancreatectomy; one of the three experienced no further hypoglycemic symptoms and two had variable symptoms, which required medical management [5].

Clancy et al. report a similar experience in two patients [6]. The first patient had reversal of her bypass initially with no improvement of symptoms. Later, she underwent an 80% pancreatectomy with good initial results. Subsequently, she developed recurrent symptoms requiring a completion pancreatectomy. The second patient had a 95% pancreatectomy and required insulin postoperatively.

Alvarez reported a laparoscopic spleen-preserving distal pancreatectomy in a postbypass patient. This patient had no symptoms during 10 months of follow-up [19].

Our results are similar: all patients have improved postoperatively, but 77% have experienced symptoms of recurrent hypoglycemia. However, their symptoms are much easier to manage than preoperatively. This is similar to the recent Mayo experience: 87% of patients experienced recurrent symptoms but were easier to manage medically (personal communication, G. Thompson, 2009). Debulking the disease seems to be beneficial.

The etiology of hypoglycemia and nesidioblastosis in this syndrome is unclear as is the association between the two. Morphology (nesidioblastosis) does not appear to correlate with physiology (hypoglycemia). There may be yet unknown factors involved. The severity of neuroglycopenic symptoms, lack of response to medical therapy, and progressive nature of disease suggest severe dysregulation of insulin secretion. One hypothesis implicates increased secretion of glucagon-like peptide 1, which is seen in increased concentration in patients with previous gastric surgery and dumping syndrome [7, 8]. Glucagon-like peptide 1 has been shown in rodents to increase the beta cell mass [20]. A subsequent increase in beta cell mass might lead to inappropriate insulin release in response to carbohydrate meal [4–6]. It also has been shown to prevent apoptosis in freshly isolated human islets [21], but there are no in vivo studies in humans. Various authors have suggested hyperinsulinemia secondary to increased beta cell mass as the cause; others disagree. Meier et al. examined pancreatic specimens from patients with postgastric bypass hypoglycemia and compared these with pancreatic specimens from obese patients as well as with specimens

obtained from lean control subjects obtained at autopsy [22]. They found no evidence of increased beta-cell formation in post gastric bypass patients. However, nuclear diameter was increased in these patients [22].

Regarding the point mentioned earlier about patients with previous gastric surgery and dumping syndrome, one of our patients, whom we excluded from this report, did not have a gastric bypass but had a previous vagotomy and pyloroplasty. This may indicate that rapid delivery of a high-carbohydrate load to the intestinal tract plays an etiologic role in the disease. Interestingly, in the 2000 Mayo study of nongastric bypass patients, approximately one third of patients had undergone some sort of previous gastric surgery [2].

There is some discussion and disagreement pertaining to the extent of pancreatic resection. Harness in 1981 reported distal pancreatectomy ranging from 50–100% [17]. Thompson et al. (2000) settled on an 80% distal pancreatectomy [2]. Witteles et al., in non-NIPHS patients, demonstrated clearly that the smaller the resection, the higher the incidence of persistent postoperative hypoglycemia. Conversely, the greater the resection, the higher the incidence of diabetes. They recommended a 60–89% resection [23]. We report an 80% resection in seven of nine patients and a 95% resection in two patients with recurrent hypoglycemia severe enough to warrant further surgery.

In conclusion, extended distal pancreatectomy (80% resection) can be safely performed laparoscopically in postgastric bypass patients with hyperinsulinemic pancreatogenous hypoglycemia who have failed medical therapy. Because the exact mechanism of disease is uncertain, we recommend caution in proceeding with pancreatectomy. However, there is a group of patients who respond to surgery, and therefore, debulking the disease appears to achieve partial or total symptom control. Patients who do not experience complete resolution of symptoms are more easily managed medically.

Disclosures Viney K. Mathavan, Maurice Arregui, Chad Davis, Kirpal Singh, Anand Patel, and James Meacham have no conflicts of interest or financial ties to disclose.

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