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Nesidioblastosis: an uncommon complication seen post Roux-en-Y gastric bypass

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Summary

Adult-onset nesidioblastosis is a rare complication of Roux-en-Y gastric bypass surgery and may occur months to years after the initial surgical procedure. It is manifested by a hyperinsulinemic, hypoglycemic state. The annual incidence of adult-onset hyperinsulinemic hypoglycemia is believed to be less than 0.1 in 1 000 000 with a mean age of onset of 47 years (1). Here, we describe a patient who presented with worsening hypoglycemic symptoms for 1 year prior to presentation that eventually progressed to hypoglycemic seizures. The onset of this hypoglycemia was 5 years after Roux-en-Y gastric bypass surgery. A full neurological evaluation, which included an EEG, head CT, and MRI, was performed to rule out epilepsy and other seizure-related disorders. After hypoglycemia was confirmed, extensive laboratory studies were obtained to elucidate the cause of the hypoglycemia and differentiate nesidioblastosis from insulinoma. Once the diagnosis of nesidioblastosis was established, a sub-total pancreatectomy was performed, and the patient was discharged and placed on acarbose, a competitive reversible inhibitor of pancreatic α-amylase and intestinal brush border α-glucosidases which slows carbohydrate absorption. The lack of information and understanding of nesidioblastosis due to its rarity makes any knowledge of this rare but important surgical complication essential. As incidence of obesity increases, the number of gastric bypasses being performed increases with it, and understanding this disease process will be essential for the primary care provider. This is the primary reason for the writing of this publication.

Learning points

- Nesidioblastosis is a persistent hyperinsulinemic, hypoglycemic state, mostly seen after Roux-en-Y gastric bypass surgery, with symptoms occurring postprandially.
- The incidence is 0.1–0.3% of all post Roux-en-Y gastric bypass patients.
- The key diagnostic clue to identifying nesidioblastosis is a positive selective arterial calcium stimulation test, showing a diffuse pattern of increased basal hepatic venous insulin concentration, whereas insulinomas would show focal increases.
- Pathological specimen of pancreas will show diffuse hypertrophy of beta cells.
- Management includes acarbose and total or subtotal pancreatectomy, which can be curative.
- With the prevalence of obesity increasing and more patients turning to Roux-en-Y gastric bypass, more patients may be at risk of this potential surgical complication.

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Background

Nesidioblastosis is a subset of noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) that results in a persistent hyperinsulinemic, hypoglycemic state, mostly seen after Roux-en-Y gastric bypass surgery (2). The incidence is not definitively known, but it is estimated to occur after 0.1–0.3% of Roux-en-Y gastric bypass procedures (3). The pathogenesis is not fully defined but is believed to be related to excessive glucagon-like peptide (GLP-1), gastric inhibitory polypeptide (GIP) and ghrelin-stimulated increases in insulin release, ultimately causing diffuse B-cell islet-cell hyperplasia (1). Histologic analysis reveals diffuse hypertrophy of beta cells on pancreatic biopsy.

The most common presenting symptoms are postprandial hypoglycemia and hypoglycemia-related complications, including seizures and loss of consciousness (4, 5, 6). The five clinical features of nesidioblastosis in adults are (i) postprandial hyperinsulinemic hypoglycemia, (ii) negative 72-h fast, (iii) negative perioperative imaging studies for insulinoma, (iv) positive calcium stimulation test and (v) islet hypertrophy or nesidioblastosis (5). Diagnosis should be suspected in a patient who presents after Roux-en-Y gastric bypass with symptoms of hypoglycemia and an elevated serum insulin and C-peptide level. Insulinoma, autoimmune causes of hyperinsulinemia and factitious hyperinsulinemia must be ruled out before a diagnosis of nesidioblastosis can be made (7, 8).

The presence of nesidioblastosis and insulinoma may be aided by employing trans-abdominal ultrasound or abdominal CT. However, these lesions are often small and typically require an extensive search for the lesion by sampling after stimulation. Additionally, when imaging is inconclusive, a positive selective arterial calcium stimulation test (SACST) showing a diffuse pattern with doubling or tripling of the basal hepatic venous serum insulin concentration indicates nesidioblastosis, whereas an insulinoma is typically associated with a focal secretion pattern (3).

Case presentation

In this report, we outline the case of a 49-year-old Caucasian female patient with a history of morbid obesity refractory to conventional treatment. Five years after undergoing Roux-en-Y gastric bypass surgery, she presented to the emergency department (ED) after a new onset of seizure. Other symptoms included episodes of flushing, facial numbness, diaphoresis, confusion, feelings of detachment and spots in her visual field. At the time of the seizure, the patient had no known history of seizures and no known triggers for new onset of seizures. Her medical history was significant for obesity, hypertension, B12 deficiency, folate deficiency and iron deficiency. Significant surgical history included hysterectomy, cholecystectomy, gastroplasty and a Roux-en-Y gastric bypass (July 2003). She used five cigarettes daily and denied alcohol use. Pertinent family history included a father who had a pancreatic cancer and diabetes. Since her Roux-en-Y gastric bypass, she experienced episodes that she characterized as hypoglycemia which occurred approximately 1.5 h post prandially. They were most common after ingestion of carbohydrate-rich foods, early in the morning or in the fasting state. Over the span of 3 years, her hypoglycemic symptoms progressively worsened and developed spontaneously, occurring three to four times weekly and with no association to food intake.

Investigation

Her initial evaluation included a CT, MRI and EEG, all of which were normal.

After structural lesions and a primary seizure disorder were excluded, an evaluation for possible hypoglycemia was undertaken. Studies performed included a 72-h fast, glucagon stimulation test, a mixed meal test, ACTH stimulation test and a sulfonylurea screen.

Relevant results included a negative 72-h fasting glucose study. After 72 h, with no symptomatic hypoglycemia, the lowest blood sugar was 56 mg/mL (reference values: 70–99 mg/dL) and beta hydroxybutyrate was 1.8 mmol (reference values: <0.4 mmol/L) (Table 1)

A glucagon stimulation test induced a rise in glucose from 56 to 62 mg/mL (reference range: an increase less than <25 mg/mL). An initial mixed meal test (MMT) was performed using liquid ensure (40 g of carbohydrate), and at 120 min post-ingestion,

Table 1 Concentration of serum beta hydroxybutyrate (mmol/L) levels after a 72-h fast. A 72 h fast is the gold standard for investigation of spontaneous hypoglycemia. Lab values above 2.7 indicate a negative fast and hypoinsulinemic state, while lab values below the reference range of 2.7 may indicate a a hyperinsulinemic state (10).

Parameter	Patient's value	Reference range (10)
Beta hydroxybutyrate, mmol/L	1.8	> 2.7

Table 2 Mixed meal test and other pertinent labs at 120 min. The initial mixed meal test (MMT) was performed using liquid ensure (40 g of carbohydrate) with measurement of glucose (mg/dL), plasma insulin (pmol/L), plasma c-peptide (pmol/L) and glucagon (pg/mL) at 120 min post-ingestion. Gold standard for detection of postprandial hypoglycemia (10).

	Patient's values	Reference range (10)	Diagnostic criteria for endogenous hyperinsulinemia (10)
Mixed meal test parameters at 120 min			
Glucose (mg/dL)	26	70–110	≤55
Plasma insulin (μIU/mL)	43 (298.74 pmol/L)	16–166	≥36 pmol/L
Plasma C-peptide (ng/mL)	13 (90.29 pmol/L)	3–9	≥200 pmol/L
Glucagon (pg/mL)	12	≤ 60	
Other pertinent labs			
Plasma sulfonylurea	Negative	Negative	Negative
Insulin antibodies	<3% bound (negative)	Negative	Negative
Plasma proinsulin (pmol/L)	–	≥5	≥5
ACTH stimulation test peak stimulation, pg/mL	28.7	10–60	
Glucagon stimulation test	A rise from 56 to 62 mg/mL	Increase less than <25 mg/mL	

ACTH, adrenocorticotropic hormone.

her serum glucose was 39 mg/dL (reference: >55 mg/dL), C-peptide was 27.78 pmol/L (reference: <200 pmol/L) and insulin was 12.50 pmol/L (reference: 20.8 pmol/L) (Table 2). It was determined that a second non-liquid MMT was indicated.

Based on her initial evaluation, further evaluation of her hypoglycemic symptoms was warranted in the following days. A mixed meal test with a mixture of carbohydrates including cheese, toast (whole wheat), milk and half of banana was performed. Post-ingestion MMT induced her symptoms and resulted in a C-peptide of 90.29 pmol/L (reference: < 200 pmol/L), glucose of 26 mg/dL (reference: >55mg/dL) and insulin of 298.64 pmol/L (reference: 20.8 pmol/L). Insulin antibody values were found to be <3% bound and CT abdomen with IV contrast revealed no pancreatic mass. Additionally, baseline CBC, CMP, liver function tests, A1C, urinalysis and insulin antibody tests were obtained and were unremarkable.

After a biochemical diagnosis was confirmed, an abdominal CT was performed to examine the pancreas. No mass was identified. A calcium stimulation test was performed via hepatic venous sampling and calcium gluconate infusion was infused in the superior mesenteric artery (SMA), gastroduodenal artery (GDA) and splenic arteries with sequential hepatic venous samples obtained for insulin (Table 3). The results of her calcium stimulation test were as follows: baseline splenic insulin value of 3.2 μIU/mL and peak value of 29 μIU/mL; baseline GDA insulin value of 1.1 μIU/mL and peak of 18 μIU/mL; baseline SMA insulin of 1.8 μIU/mL and peak of 11 μIU/mL (Table 3). These studies confirmed nesidioblastosis.

Treatment

After the Roux-en-Y surgery, the patient was empirically instructed to avoid carbohydrate-rich meals. When the patient initially presented with symptoms of possible hypoglycemia, further conservative management with additional dietary modification of balanced meals with a restricted carbohydrate component was tried, but these dietary changes did not resolve her symptoms. Because

Table 3 Selective arterial calcium stimulation test (SACST) used to differentiate nesidioblastosis from insulinoma (1). The SACST test requires cannulation of the femoral vein and artery with passage of a sampling catheter to the splenic artery, gastroduodenal artery and superior mesenteric artery to detect insulin with samples sequentially drawn from the hepatic vein (1).

Parameter	Patient's lab value	Positive/negative findings
Insulin, SP basal	3.2 uIU/mL	–
Insulin, SP 40	15 uIU/mL	Positive
Insulin, SP 60	29 uIU/mL (peak)	Positive
Insulin, GDA basal	1.1 uIU/mL	–
Insulin, GDA 40	18 uIU/mL (peak)	Positive
Insulin, GDA 60	13 uIU/mL	Positive
Insulin, SMA basal	1.8 uIU/mL	–
Insulin, SMA 40	7.1 uIU/mL	Positive
Insulin, 60	11 uIU/mL (peak)	Positive

GDA, gastroduodenal artery; SMA, superior mesenteric artery; SP, splenic artery.

the patient had experienced continued, profound, hypoglycemia with significant complications, further intervention was determined to be necessary. A reversal/modification of Roux-en-Y surgery was then discussed as an option but was refused by the patient at the time of the suspected, and subsequently confirmed, diagnosis of nesidioblastosis.

Following these discussions, the patient underwent an extended distal pancreatectomy with splenectomy, a small bowel resection of the blind Roux limb loop and an intraoperative pancreatic ultrasonography. Examination of the pathological specimen showed moderate islet hypertrophy with nuclear enlargement. After this procedure, the patient was treated with acarbose of 50 mg p.o. with each meal.

Outcome and follow-up

Following the subtotal distal pancreatectomy, the patient was treated with acarbose 50 mg p.o. with each meal and the patient's symptoms resolved completely. The patient has been carefully monitored for the course of 14 years and has remained symptom free.

Discussion

Nesidioblastosis is currently a rarely identified complication of Roux-en-Y gastric bypass surgery, but with the rates of obesity and bariatric surgery on the rise, the prevalence of this complication may subsequently increase. This condition typically presents with a hyperinsulinemic, hypoglycemic state with symptoms, such as seizures, diaphoresis and altered mental status, caused by the low serum glucose levels (2, 3, 4). Chronic dumping syndrome and insulinoma must be excluded. Abdominal CT or ultrasound may help differentiate among the endogenous causes of a high insulin, low glucose state. A definitive diagnosis is made using a combination of biochemical and imaging studies (5, 9). Management of nesidioblastosis includes the use of acarbose and, when refractory to medical therapy, a total or sub-total pancreatectomy may be indicated but can be curative as demonstrated in this case (5, 7, 9)

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

Author contribution statement
K Kim is the primary author of this manuscript; J L Greenspan was responsible for writing, reviewing and editing the manuscript; S Mehrara was responsible for reviewing and editing the manuscript; D Wynne oversaw the patient care and supervised in the writing and editing of this manuscript; E Ennis provided endocrinology diagnostics, clinical care and supervised writing and editing the manuscript.

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