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CASE REPORT

An unusual cause of hypoglycemia in a middle-aged female after bariatric surgery

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Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a disorder characterized by postprandial hypoglycemia and islet cell hypertrophy. It is an uncommon complication of weight-loss surgery. However, with the rising incidence of gastric bypass surgeries, it is important to be able to recognize the clinical picture of NIPHS and not to incorrectly ascribe the symptoms to late dumping syndrome.

Keywords: *NIPHS*; *postprandial hypoglycemia*; *nesidioblastosis*; *gastric bypass surgery*

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A 47-year-old morbidly obese female (BMI 42.2 kg/m^2) with a medical history of well-controlled type 2 diabetes mellitus (A1C 5.6%) and hypertension presented with a 2-month history of progressively worsening, recurrent episodes of postprandial hypoglycemia. She had undergone Roux-En-Y gastric bypass surgery 8 months prior for morbid obesity. She lost about 100 pounds after the surgery from an earlier weight of 360 pounds. She reported symptoms of weakness, dizziness, and sweating within 2–3 hours of eating, with fingerstick glucose levels of 60–70 mg/dl during these episodes. Symptoms resolved with intake of sugar. She denied similar symptoms in the fasting state. Her blood sugar levels in the morning and between the episodes were normal, and, in fact, she no longer met criteria for a diagnosis of diabetes, and had been off all treatment even before the surgery. She denied using insulin, oral hypoglycemics, or drinking excessive alcohol. There was no history of abdominal pain or diarrhea. On examination, vital signs were notable for elevated blood pressure (173/94 mmHg) with normal pulse rate (59/minute). The remainder of the physical examination was unremarkable.

Initial laboratory results, including fasting C-peptide, insulin, and blood glucose, were all normal. The 75 g oral glucose tolerance test revealed elevated insulin and C-peptide levels at 1, 2, and 3 hours (Table 1). Urine sulfonylurea and meglitidine screening was negative. Computed tomography (CT) of the abdomen and abdominal magnetic resonance imaging (MRI) showed no focal abnormalities of the pancreas.

The patient began dietary modification with a reduction in carbohydrate in her diet for possible dumping syndrome. As this did not resolve her symptoms, she was then started on acarbose and verapamil. However, she continued to have worsening hypoglycemic symptoms. Therefore, she was evaluated further for non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS).

Selective arterial catheterization and calcium stimulation testing was performed. This indicated increased insulin secretion throughout the pancreas, which suggested diffuse beta cell hyperplasia. However, the bulk of stimulated insulin production was from the distal body and tail of the gland. Given this distal predominance, she underwent distal pancreatectomy. Histopathological examination of the pancreatic specimen revealed varying sized islets and scattered ductulo-insular complexes, was suggestive of nesidioblastosis. There was no evidence of insulinoma.

Her hypoglycemic symptoms were successfully relieved after the surgery. However, several months after the surgery, despite her weight remaining stable, she developed significant fasting and postprandial hyperglycemia, and required the re-initiation of treatment with metformin and insulin therapy.

Discussion

NIPHS is a syndrome characterized by hypoglycemia caused by increased insulin secretion from pancreatic beta cell hyperplasia. The diagnosis is based on exclusion

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Table 1. Serial insulin and C-peptide levels in our patient after 75 g oral glucose load

	Serum glucose (mg/dl)	Insulin levels ($N = 1–14$ mIU/ml)	C-peptide levels ($N = 0.9–4.3$ ng/ml)
Fasting	87	5.4	2.5
1 hour	196	156	18
2 hour	126	35.3	13
3 hour	64	7.6	6.3

of insulinoma and dumping syndrome by laboratory evaluation and histopathological examination of the pancreas (1). In our patient, we were able to exclude insulinoma due to the absence of fasting hypoglycemia with normal insulin, proinsulin, C-peptide levels, and negative imaging studies of the pancreas (2). However, NIPHS can be easily confused with late dumping syndrome.

Late dumping syndrome is a common delayed complication of bariatric surgery characterized by reactive hypoglycemia secondary to postprandial insulin surge. Symptoms such as weakness, sweating, and dizziness appear 2–3 hours after meals and occur a few months after surgery. Symptoms usually improve after a few months with dietary modifications. Recommended dietary modifications include decreasing the amount of simple carbohydrates and excluding fluid intake during ingestion of the solid portion of the meal (3). The onset of symptoms more than 6 months after her gastric bypass surgery and a lack of improvement with dietary modifications made late dumping syndrome unlikely in our patient.

NIPHS is differentiated from solitary insulinoma by diffuse calcium-stimulated hyperinsulinism from multiple segments of pancreatic vascular anatomy on selective arterial calcium stimulation test (SACST) (4). In our patient, SACST revealed diffuse insulin hypersecretion, with the bulk of the production from the body and tail of the pancreas, thus confirming the diagnosis of NIPHS.

NIPHS was first reported and described by Service et al. (5). Various hypotheses have been proposed for the cause of islet cell hyperplasia following Roux-en-Y bypass surgery. Current thinking is focusing on the rapid hormonal changes involving insulin-stimulating GLP-1 (glucagon-like peptide-1) and decreased ghrelin with hyperinsulinemia and rapid weight loss (6–8).

Most patients with mild to moderate symptoms of hypoglycemia respond well to dietary modifications (9). Patients that are refractory to a low carbohydrate diet can be treated with the alpha-glucosidase inhibitor acarbose, verapamil, and/or diazoxide (10, 11). Gradient-guided surgical resection of the pancreas is the definitive treatment for NIPHS with symptoms persisting despite medical treatment (12).

Conclusion

NIPHS should be suspected as a cause of postprandial hypoglycemia in patients with gastric bypass surgery if they present with recurrent and severe postprandial hypoglycemia without fasting hypoglycemia. Diagnosis of this syndrome requires detection of endogenous hyperinsulinemic hypoglycemia, positive SACST and negative localization studies for insulinoma. Dietary therapy and pharmacological treatment with acarbose, verapamil, and octreotide can be tried initially for mild to moderate symptoms while patients with severe symptoms eventually need gradient guided partial or total pancreatectomy.

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