DIABETICMedicine

DOI: 10.1111/dme.12571

Case Report

Histological insights into the pathogenesis of post-Roux-en-Y hyperinsulinaemic hypoglycaemia

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Accepted 22 August 2014

Abstract

Background β-cell hyperplasia has been implicated in the aetiology of post Roux-en-Y gastric bypass hyperinsulinaemic hypoglycaemia, but the pathogenesis of this condition is still unclear.

Case report We report a case of a 52-year-old man with post-Roux-en-Y gastric bypass hyperinsulinaemic hypoglycaemia who underwent distal pancreatectomy to alleviate his symptoms. Pancreatic histopathology showed chronic pancreatitis with a corresponding loss of exocrine tissue and islet retention. Amyloid deposition was found in pancreatic islets. These features are more typically associated with Type 2 diabetes.

Discussion This case highlights the potential multifactorial pathogenesis of symptomatic hypoglycaemia after Roux-en-Y gastric bypass.

Diabet. Med. 31, e29–e32 (2014)

Introduction

Hyperinsulinaemic hypoglycaemia is a rare complication of Roux-en-Y gastric bypass. β-cell hyperplasia has been implicated and ascribed to excessive glucagon-like peptide-1 secretion [1–3]; however, this hypothesis has been subject to debate, as other groups have shown similar histological findings in patients without hypoglycaemia [4]. In the present report we present a patient with this condition who was found to have pancreatic histology typically associated with Type 2 diabetes.

Materials and methods

Histopathological studies were carried out at the Department of Pathology, University of Michigan. Haematoxylin and eosin staining was performed on pancreatic sections that had been formalin fixed and paraffin embedded. For immunohistochemistry, pancreatic sections were incubated with either rabbit polyclonal antiglucagon or rabbit polyclonal anti-insulin antibodies from Ventana Medical Systems (Basel, Switzerland).

Case report

A 52-year-old man was evaluated for recurrent episodes of hypoglycaemia for 6 months. He reported multiple episodes of hypoglycaemia during the night, in the early morning and > 4 hours after meals. He had had insulin-treated Type 2 diabetes mellitus for 10 years until 2003, when he underwent a Roux-en-Y gastric bypass and total gastrectomy (see below) for morbid obesity and diabetes. Shortly after the surgery, insulin was withdrawn as a result of improvement in glycaemic control and he subsequently lost 50 kg in weight. Since 2005 he has experienced recurrent episodes of fasting hypoglycaemia (1.6–2.2 mmol/l or 30–40 mg/dl), accompanied by neuroglycopenic symptoms (lethargy and disorientation) and aborted with glucose intake (Whipple's triad). To avoid hypoglycaemia, he had been eating frequently and had gained weight. A therapeutic trial with a combination of somatostatin analogue and diazoxide failed to alleviate his symptoms. α-glucosidase inhibitor was not given because of the patient's chronic gastrointestinal symptoms and a calcium blocker was not given because of his low blood pressure [5].

The patient's medical history was noteworthy for gastro-oesophageal reflux disease treated with Nissen's fundoplication in 2000 and pantoprazole. The patient did not develop hypoglycaemia after fundoplication [6]. The patient has had undergone gastrectomy with Roux-en-Y anastomosis in 2003 and the operation was expanded to total gastrectomy because of incidental finding of gastric polyps. The histology was found to be benign. Diabetic autonomic and sensory neuropathy, manifested by feet numbness and colonic dysmo-

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What's new?

- We present a case of a patient with post Roux-en-Y hypoglycaemia and pancreatic histology typically associated with diabetes.
- We show that hyperinsulinaemic hypoglycaemia has a multifactorial aetiology.

tility (bowel movement every 2 weeks) for which total colectomy was contemplated; hyperlipidaemia, treated with atorvastatin; epilepsy; bipolar disorder; sleep apnoea syndrome; asthma; benign prostatic hypertrophy; osteoarthritis; asbestosis; and urolithiasis and the patient had previously undergone cholecystectomy. The patient did not consume alcohol. None of his medications were expected to alter his carbohydrate metabolism. His physical examination was normal except for temporal wasting (weight 88 kg, height 175 cm, BMI 29 kg/m^2). The patient's blood count, biochemical profile, thyroid functions, lipase and amylase were normal.

The results of two fasting studies, administered 3 months apart, showed endogenous insulin-dependent hypoglycaemia. In the first test, the patient developed symptomatic hypoglycaemia at 3.3 mmol/l (60 mg/dl) after a 48-h fast, while plasma insulin and C-peptide levels were 64.2 pmol/l (10.7 mcu/ml) and 0.6 nmol/l (1.7 ng/ml), respectively. During the second fasting test, the patient developed hypoglycaemia at 2 mmol/l (36 mg/dl) after a 4-h fast, while plasma insulin, proinsulin and C-peptide levels were 46.8 pmol/l (7.8 mcu/ml), 9.7 pmol/l and 0.4 nmol/l (1.3 ng/ml), respectively. Abnormal was defined as insulin level ≥ 36 pmol/l (≥ 6 mcu/ml), proinsulin level ≥ 5 pmol/l and C-peptide level or ≥ 0.2 nmol/l (≥ 0.6 ng/ml) [7]. Blood screens for oral hypoglycaemic agents were negative. Transoesophageal ultrasonography did not show pancreatic lesions. Abdominal magnetic resonance imaging showed a 6-mm contrast-enhancing lesion in the pancreatic head and a few 5-mm foci in the liver. Both lesions were found to be stable in periodic imaging. A 111-indium octreotide scan was negative. The results of selective intra-arterial calcium stimulation with hepatic venous sampling are shown in Fig. 1. The test showed a 2–3-fold rise in plasma insulin and a 1.3–2-fold rise in plasma C-peptide levels, after calcium stimulation of the splenic, gastroduodenal, common hepatic and superior mesenteric arteries with a peak detected after 60 s. Injection of calcium to the proper hepatic artery (control) did not change insulin and C-peptide levels in the hepatic vein. The test was interpreted as abnormal with mild oversecretion of insulin from the entire pancreas.

The complete clinical picture was felt to be consistent with non-insulinoma pancreatogenous hypoglycaemia, secondary to Roux-en-Y anastomosis. In January 2007, the patient underwent total colectomy and ileosigmoid anastomosis (to alleviate his chronic constipation), distal pancreatectomy (50% of the pancreas) to alleviate his hypoglycaemia [3] and splenectomy. The pancreas was dissected adjacent to the superior mesenteric vein. In gross pathology the cut surface of the pancreas was not found to harbour tumours. Histopathology was taken from multiple locations and identified pancreatitis with a corresponding loss of exocrine pancreatic tissue and islet retention (Fig. 2a), amyloid deposition within pancreatic islets (Fig. 2b) and incidental low-grade dysplasia of ductal epithelium. Distributions of β and α cells were normal (Fig. 2c and 2d).

Less than 1 month after the operation the patient's hypoglycaemia relapsed with glucose readings of 2.5–3.3 mmol/l (45–60 mg/dl). Yet, in contrast to the pre-surgery period, his hypoglycaemia had been successfully controlled [readings > 3.3 mmol/L (> 60 mg/dl)] with a combination of diazoxide 150–200 mg 3–4 times per day and lanreotide 80 mg every 4 weeks (similar to his pre-surgery doses).

Discussion

The presented patient exhibits an atypical case of post-gastric bypass hyperinsulinaemic hypoglycaemia. Although previous reports have mainly described postprandial symptoms, some have described severe cases of neuroglycopenia that occurred also before meals or required continuous glucose infusion [8]. In these cases, the differentiation betweenpreprandial and postprandial periods is vague. Moreover, excessive glucagon-like peptide 1 secretion has been implicated in this condition [1–3] and shown to occur both before and after meals [9]. It is not improbable that the patient may have developed delayed postprandial hypoglycaemia as a result of gastrointestinal dysmotility. Evidently, during his second fasting test, hypoglycaemia occurred 4 h after eating. Several clinical details clearly support the relevance of our report to the post-gastric bypass state. As expected, hypoglycaemia started a few years after the gastric bypass [3], a fasting test identified endogenous hyperinsulinaemia, selective arterial calcium stimulation showed generalized pancreatic hyperinsulinaemia and cross-sectional studies and pathological examination did not identify insulinoma.

Instead of an abundance of β-cell mass as expected in this setting [3], pancreatic histology showed chronic pancreatitis and pancreatic islets amyloidosis. Both histological findings and their corresponding medical conditions are expected to cause insulin deficiency and hyperglycaemia. While a number of groups have reported an abundance of pancreatic islets and periductal beta-cell budding compared to controls [3] other groups have failed to substantiate these findings [10].

Amyloid deposition in pancreatic islets, derived from islet amyloid polypeptide or amylin is traditionally implicated with longstanding Type 2 diabetes [11] and, to the best of our knowledge, has not been described after diabetes

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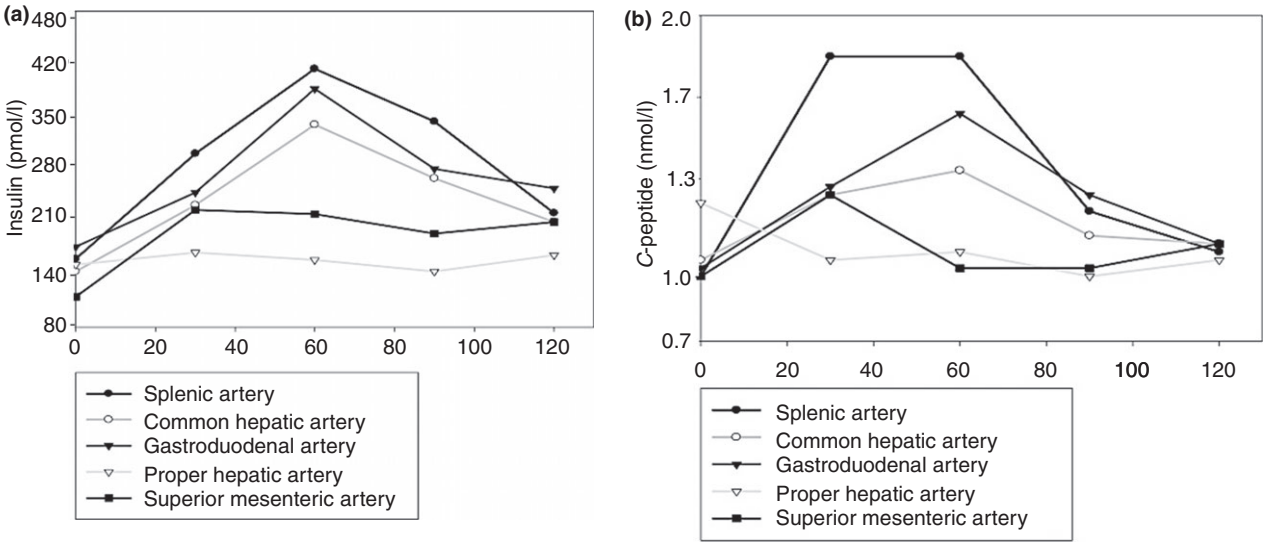

FIGURE 1 Selective intra-arterial calcium stimulation with hepatic venous sampling (as previously described [15]). a) Insulin. b) C-peptide. Intravascular catheters were inserted via the femoral artery and femoral vein.

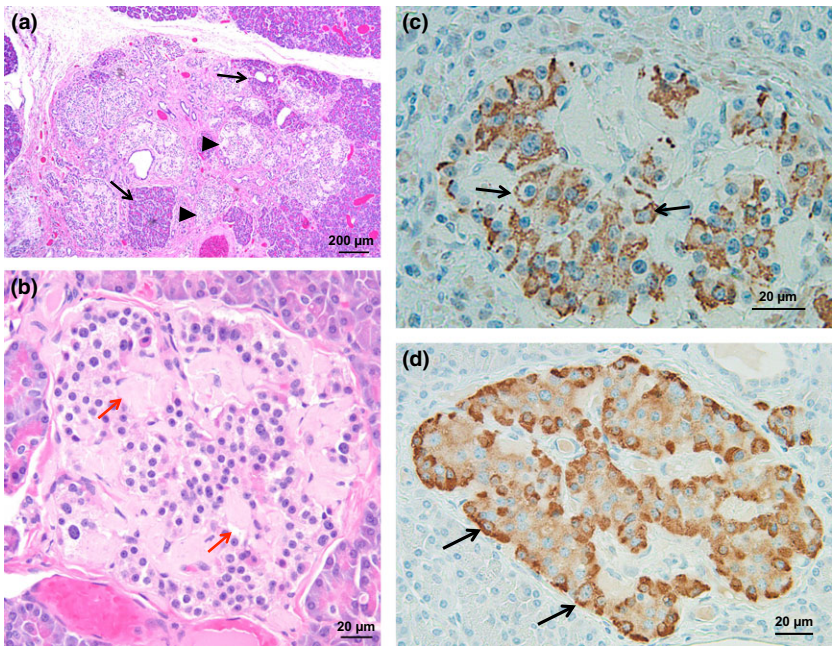

FIGURE 2 Representative histopathology of pancreatic tissue. a) Chronic pancreatitis with loss of exocrine tissue and collapse of lobule architecture. Remnant acinar tissue (black arrows) and islets of Langerhans (black arrowheads) are surrounded by connective tissue with minimal lymphocytes. Haematoxylin and eosin-stained pancreatic section. b) Representative islet of Langerhans with amyloid deposition. Amyloid tufts (red arrows) are embedded between endocrine cells. Haematoxylin and eosin-stained pancreatic section. c) Insulin immunohistochemistry. Representative pancreatic islet with amyloid deposition. β cells (arrows) comprise the majority of the endocrine cells in a typical distribution. d) Glucagon immunohistochemistry. Representative pancreatic islet showing α cells (arrows) in a typical frequency and distribution.

remission. These deposits have been detected also in patients with insulinoma [12,13]. In these cases amylin is probably over- synthesized alongside insulin and ultimately forms amyloid tufts. Recurrent hypoglycaemia and brittle diabetes pattern is seen in patients treated with insulin for pancreatitis-associated diabetes and these have been explained by glucagon deficiency and maldigestion [14].

We hypothesize that the patient in the present report may have developed recurrent hypoglycaemia as a result of hyperinsulinaemia (evidenced by his biochemical profile

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and islets amyloid), potentially combined with glucagon deficiency and carbohydrate maldigestion (resulting from chronic pancreatitis). Pancreatitis may not have inflicted pain owing to autonomic neuropathy. It is possible that undergoing total gastrectomy during his gastric bypass had exposed him to a shortened food passage and thus made absorption even more difficult. Partial pancreatectomy may have alleviated his hypoglycaemia but not cured it, as the surgical procedure decreased β-cell mass but would not have improved glucagon deficiency or carbohydrate maldigestion. Additional metabolic insults (e.g. chronic pancreatitis, malabsorption, dumping syndrome) may be needed to tip the balance of a patient's homeostasis toward hypoglycaemia.

Funding sources

None.

Competing interests

None declared.

Acknowledgements

The authors thank Bill and Dee Brehm for improving diabetes research infrastructure at the University of Michigan. This work was supported by the Michigan Center for Diabetes Translational Research, grant number P30DK092926, and the National Institute of Diabetes and Digestive and Kidney Diseases.

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