Rare disease

A rare case of non-insulinoma pancreatic hypoglycaemia syndrome (niphs) in an adult due to localised islet cell hyperplasia—successfully managed by enucleation

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Summary

Persistent hyperinsulinemic hypoglycaemia is caused most commonly by an insulinoma in adults or by nesidioblastosis in neonates. In adults, localised islet cell hyperplasia is a rare disorder characterised by localised proliferation of islet cells. The authors present the case of a previously healthy non-obese middle aged female with new-onset severe hypoglycaemia. Laboratory findings confirmed a case of hyperinsulinemic hypoglycaemia. Endoscopic ultrasonography, intra-arterial calcium stimulation test and intraoperative ultrasonography showed a lesion in the uncinate process that was enucleated. Rest of the pancreas was normal. Histological examination and immunostaining of the resected tissue revealed pancreatic tissue with maintained acinar pattern consistent with diagnosis of localised islet cell hyperplasia. The patient did not have further episodes of hypoglycaemia following the procedure. Localised islet cell hyperplasia with such a very high insulin level is exceedingly rare in adult populations and not reported in literature. This diagnosis cannot be easily made through routine diagnostic laboratory or radiological procedures and likely requires a histological diagnosis. Management of this rare entity is by enucleation.

BACKGROUND

- (1) This young middle aged non-obese female with recent onset recurrent hypoglycaemia on evaluation found to have non-insulinoma pancreatic hypoglycaemia due to localised islet cell hyperplasia managed successfully with enucleation.
- (2) Possibility of insulin autoantibody syndrome was excluded in view of negative antibody.
- (3) Non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) due to islet cell hyperplasia is very

uncommon in adult as it is comparatively common in paediatric age group.

- (4) Islet cell hyperplasia in localised form is extremely rare variant which was established in our case with endoscopic ultrasonography (EUS), selective intra-arterial calcium injection, intraoperative ultrasonography.
- (5) Patient was successfully managed with enucleation avoiding the more extensive subtotal pancreatic resection for islet cell hyperplasia of diffuse variant.

Figure 1 Photomicrograph (x400) showing islet cell hyperplasia without nesidioblastosis (H and E staining).

Figure 2 Photomicrograph (x100) showing islet cell hyperplasia without nesidioblastosis (H and E staining).

Figure 3 Photomicrograph (x100)—Islet cell shows positivity for synaptophysin.

Figure 4 Photomicrograph of pancreas (x100)—Islet cell shows positivity for chromogranin.

- (6) Postoperative follow-up of the patient there was no occurrence of hypoglycaemic symptoms in this patient.
- (7) NIPHS due to localised islet hyperplasia can lead to recurrent hypoglycaemia symptoms. Need for establishing this diagnosis is essential as limited resection surgery can cure this disease, which avoids the complications of more extensive surgery.

CASE PRESENTATION

The presenting case is a 45-year-old female patient who was admitted to medicine emergency with impaired consciousness of 2 h duration. She was found to be hypoglycaemic (random blood sugar 1.3 mmol/litre) and her symptoms improved after infusion of 25% dextrose. This was the first time that she had these symptoms. Over the next 24 h of her hospital stay, she developed recurrent episodes of hypoglycaemia despite good oral intake and required continuous infusion of glucose. She was neither a known diabetic nor hypertensive nor taking any other medications. There were no nocturnal symptoms and no history of weight loss, abdominal pain or diarrhoea. She denied the use of oral hypoglycaemic agents or insulin. Examination revealed a haemodynamically stable patient with an unremarkable systemic examination. Endocrine system examination excluded hypopituitarism and adrenal insufficiency as causes of her hypoglycaemia.

INVESTIGATIONS

Laboratory tests were essentially normal with the exception of hypoglycaemia. Blood sampling during hypoglycaemic episodes revealed an inappropriately high insulin level of 810 mIU/ml with insulin-glucose ratio of 58 and a high C-peptide level of 15 ng/ml (normal 0.5–2.0 ng/ml). Contrast-enhanced CT scan, MRI and celiac angiography did not reveal any pancreatic mass lesion. Anti-insulin autoantibodies were negative. Sulphonylurea screen was negative.

Further investigations were ordered to exclude the possibility of an occult insulinoma. EUS revealed a hyperechoic mass lesion in the head of the pancreas measuring 1.5×1.5 cm. The patient was subjected to selective arterial

calcium injection (SACI) to rule out other sites of involvement. After injection of calcium gluconate (0.05 mg/kg body weight) into splenic, gastroduodenal and superior mesenteric arteries, blood samples were collected from the right hepatic vein every 30 s for 120 s. Following SACI into the gastroduodenal and superior mesenteric arteries, there was a 12-fold increase in insulin levels and a fivefold increase in C-peptide levels. Histopathological and immunohistochemical staining of the resected pancreas tissue revealed a maintained acinar pattern with an increase in islet cell population (figures 1 and 2). There is only increase in population of β cells without high mitotic index and angioinvasion. On immunostaining, it was stained positively for chromogranin-A, synaptophysin and insulin (figures 3–6) (table 1). Immunohistochemical staining revealed an increase in the number of insulin-secreting β cells. The findings were consistent with a pathological diagnosis of islet cell hyperplasia.

DIFFERENTIAL DIAGNOSIS

- ▶ Insulin autoantibody syndrome
- ▶ Sulphonylurea induced hypoglycaemia
- ▶ Insulinoma.

TREATMENT

Under the presumptive diagnosis of insulinoma localised to head of pancreas based on EUS and SACI reports, surgical exploration was performed. Careful palpation and intraoperative ultrasonography revealed a hyperechoic mass localised to the uncinate process and enucleation of the tumour was done. Postoperative course was uneventful and her plasma glucose remained between 5–6.5 mmol/l without glucose infusions. The patient no longer experienced any hypoglycaemic episodes. She is currently free from either hypoglycaemia or hyperglycaemia.

Histopathological and immunohistochemical staining of the resected pancreas tissue revealed a maintained acinar pattern with an increase in islet cell population (figures 1 and 2). There is only increase in population of β cells without high mitotic index and angioinvasion. On immunostaining, it was stained positively for chromogranin-A, synaptophysin and insulin (figures 3–6)

Figure 5 Photomicrograph (x100)—Islet cell shows positivity for insulin.

Figure 6 Photomicrograph (x400) Islet cell show strong positivity for insulin

Table 1 Immunostaining of resected specimen of pancreatic tissue

Immunostaining	Endocrine pancreas	Exocrine pancreas
Insulin	Strongly positive	Negative
Chromogranin	Positive	Negative
Synaptophysin	Positive	Negative

(table 1). Immunohistochemical staining revealed an increase in the number of insulin-secreting β cells. The findings were consistent with a pathological diagnosis of islet cell hyperplasia.

OUTCOME AND FOLLOW-UP

Careful palpation and intraoperative ultrasonography revealed a hyperechoic mass localised to the uncinate process and enucleation of the tumour was done. Postoperative course was uneventful and her plasma glucose remained between 5–6.5 mmol/litre without glucose infusions. The patient no longer experienced any hypoglycaemic episodes. She is currently free from either hypoglycaemia or hyperglycaemia.

DISCUSSION

Hypoglycaemia is a common medical emergency. Among hospitalised patients, it is most common in those with diabetes, but also occurs in patients with renal insufficiency, liver disease, malnutrition, congestive heart failure, sepsis, or cancer. Diabetes on treatment with insulin is an important cause of hypoglycaemia among ambulatory groups.^{1 2} Factitious or surreptitious use of insulin or sulphonylurea drugs is probably one of the most common cause of hypoglycaemia among patients who do not have diabetes.^{3 4} However, these above mentioned common causes of hypoglycaemia in this case was excluded in view of normal laboratory finding and no evidence of exogenous insulin and sulphonylurea intake. When these common causes are excluded, insulinoma is the most common cause of hyperinsulinemic hypoglycaemia. Nesidioblastosis is a rare but well-recognised disease causing persistent hyperinsulinemic hypoglycaemia in infancy, but is rarely reported in adults (0.5–5% of organic causes).^{5 6} However, adult-

onset localised islet cell hyperplasia as a cause of persistent hyperinsulinemic hypoglycaemia in adults is not reported in literature.

The first case of hyperinsulinemic hypoglycaemia due to an insulinoma that was successfully treated by surgery was reported in world literature in 1929.⁷ Over the last few years, another disease with high endogenous insulin production and hypoglycaemia has been identified.² This disease was called NIPHS. It differs from insulinoma by the time of occurrence of hypoglycaemia. In patients with insulinoma, hypoglycaemia usually occurs during fasting but in NIPHS there is reactive hypoglycaemia.⁸

All radiological investigations for localisation of a lesion are supposed to be normal in patients diagnosed to have NIPHS. This patient with NIPHS had a lesion that was demonstrated in the head of the pancreas by EUS. Intraoperative ultrasonography showed the lesion to be in the uncinate process of the pancreas, which corresponded to the location of the pathology.^{9 10}

SACI is a reliable test for the localisation of insulinoma. One report evaluated 24 patients with proven hyperinsulinemia.¹¹ Seven of these patients had negative morphologic studies. At surgery, six had an insulinoma and one had nodular hyperplasia. In all seven patients, calcium infusion permitted localisation of the source of insulin secretion.¹²

In the case in question, the positive response following an injection into the superior mesenteric and gastroduodenal arteries and EUS findings of a hyperechoic lesion in the head of pancreas localises the insulinoma to the head of pancreas. However, after surgical exploration and enucleation, the surgical specimen was consistent with islet cell hyperplasia without nesidioblastosis on histopathological examination. Intraoperative ultrasonography of the rest of the pancreas was normal.

The treatment of NIPHS is by surgery. The extent of surgery is determined by the results of the SACI test. Partial pancreatectomy resulted in successful treatment of hypoglycaemia in most of the cases reported. Some patients still continued to have episodes of hypoglycaemia following surgery, which most likely was due to a diffuse islet cell hyperplasia requiring a complete pancreatectomy.¹³

This patient improved after partial pancreatectomy, without any further episodes of hypoglycaemia.

Patients with similar lesions should undergo localisation of the source of insulin production by the stimulation test and should be treated by partial pancreatectomy rather than total pancreatectomy. This will reduce the incidence of diabetes mellitus after surgery.

Learning points

- ▶ Islet cell hyperplasia in localised form is extremely rare variant and rare cause of hypoglycaemia, the diagnosis of which can be established with EUS, selective intra-arterial calcium injection, intraoperative ultrasonography.
- ▶ Patient was successfully managed with enucleation avoiding the more extensive subtotal pancreatic resection for islet cell hyperplasia of diffuse variant.
- ▶ NIPHS due to localised islet hyperplasia can lead to recurrent hypoglycaemia symptoms. Need for establishing this diagnosis is essential as limited resection surgery can cure this disease, which avoids the complications of more extensive surgery.

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Competing interests None.

Patient consent Obtained.

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