An Insulinoma for which Secretin Test and Selective Arterial Calcium Injection Test were Useful

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Abstract

A 76-year-old woman suffered from somnolence while fasting for almost 2 years. Fasting plasma glucose (FPG) (40 mg/dl) and the immunoreactive insulin (IRI) level (8.8 µU/ml) were not compatible with Fajan’s ratio or Turner’s ratio observed in typical insulinoma. The secretin test showed no response to insulin secretion, suggesting the presence of insulinoma. Abdominal dynamic computed tomography (CT) revealed a 12-mm hypervascular lesion in the head of the pancreas. A selective arterial calcium infusion test (SACI) was performed, during which IRI in the hepatic venous blood was measured following selective intraarterial calcium infusion. An increase in IRI levels in the gastroduodenal and superior mesenteric arteries suggested the presence of a functional insulinoma in the head of the pancreas. Enucleation of the tumor improved FPG and IRI levels to 138 mg/dl and 3.8 µU/ml, respectively. After surgery, a secretin test showed a 5-fold increase in IRI levels, suggesting normal β cell function. This case illustrates the value of the secretin test for the diagnosis of insulinoma and for the postoperative assessment of β cell function. It further illustrates the value of the SACI for localizing an insulinoma.

Key words: pancreas tumor, hypoglycemia, β cell function

Introduction

It is often difficult to confirm that hypoglycemia results from insulinoma. Neither Fajan’s (IRI/FPG) or Turner’s (IRI×100/(PG-30)) ratios for hormonal assessment nor imaging diagnostics such as angiography or dynamic computed tomography (CT) provide sufficiently high sensitivity for the diagnosis of insulinoma. Imaging techniques are frequently unable to detect a significant percentage of insulinomas [CT, 52.4%; angiography, 69.5%; ultrasound (US), 43.9%; magnetic resonance imaging (MRI), 72.7%]. Such difficulty may be due to characteristics of insulinoma; 81.1% of cases are within 2 cm in size, with a 6.6% rate of metastases, and 12.6% of cases have multiple lesions (1).

This report describes a case in which a secretin test (2) was used to diagnose an insulinoma, and Selective Arterial Calcium Infusion test (SACI) (3) was used for assessing location and function of the tumor. The secretin test was also used post-surgically to confirm complete resection of tumor and to assess the recovery of remaining β cell function.

Case Report

A 76-year-old woman suffered from somnolence before breakfast for almost 2 years. The morning somnolence occurred about once in two months. Normal consciousness was consistently recovered following sugar intake. No remarkable past history was found. She had one son who had diabetes treated with voglibose for 5 years.

In June 2000, the patient was admitted to Osaka City Kita Hospital for evaluation of her morning, pre-prandial somnolence. Early in the morning, her fasting plasma glucose (FPG) was 31 mg/dl and her immunoreactive insulin (IRI) was 7.0 µU/ml. Plasma IRI level was not sufficiently high to apply the classical criteria for insulinoma, Fajan’s ratio (IRI/FPG ≤ 0.3) or Turner’s ratio (IRI×100/(PG-30) ≤ 200). Counterregulatory hormones including catecholamines, glucagon, thyroid hormone and growth hormone were within normal limits. During episodes of hypoglycemia, the patient moved sluggishly. However, she exhibited no other symptoms of hypoglycemia, such as diaphoresis, tremor or palpitations.
Both the glucagon injection test and 75 g oral glucose tolerance test (OGTT) revealed persistently high plasma levels of IRI (Fig. 1). The secretin test was subsequently performed, involving intravenous injection of 2 U/kg of secretin followed by peripheral venous sampling at 2, 4 and 6 minutes post-injection for IRI level measurement. Secretin injection prompted no increase in plasma IRI, a finding compatible with insulinoma. Dynamic CT scanning revealed a 12-mm hypervascular tumor in the head of the pancreas. To insure accurate preoperative tumor localization and to further assess tumor function, a selective arterial calcium injection (SACI) test was performed, via the transcutaneous femoral artery (Fig. 2). This test is usually performed at the time of selective abdominal arteriography. A 5-ml bolus of 0.025 mEq Ca²⁺/kg of calcium gluconate diluted with saline was injected into each of the following: the gastroduodenal artery (GDA), superior mesenteric artery (SMA), splenic artery (SA), and right hepatic artery (RHA). Blood samples from the right hepatic vein were taken prior to and at 30, 60, 90 and 120 seconds post-injection in order to measure IRI levels. A marked increase in IRI levels was observed in the GDA and SMA, with no change in IRI levels in the SA and RHA (Fig. 2). These results suggested an insulinoma located on the head of pancreas, with no metastases to other locations, such as the tail of the pancreas or the liver. Simultaneous angiography showed a single tumor fed by both the GDA and SMA.

Enucleation of the tumor was performed on the twentieth hospital day. Plasma glucose level recovered to within the normal range soon after the enucleation. No episode of hypoglycemia was observed after the operation. On the eighteenth postoperative day, a glucagon test showed the normal IRI response. Administration of 75 g OGTT revealed an IGT pattern. On the twenty-first postoperative day, a secretin test was performed, prompting an almost 5-fold increase in IRI levels, suggesting a normal β cell response. Pathohistological examination revealed the tumor to be an islet cell adenoma. Immunohistological examination showed that the tumor expressed insulin, but not glucagon, somatostatin, or gastrin.

Discussion

In recent years, it has been reported that hormonal data in many cases of insulinoma may not be compatible with the classical Fajan’s ratio or Turner’s ratio (4). This may be due to the specificity of the antibody used for measurement. Because the antibodies used might not distinguish between insulin and pro-insulin, the IRI level may be overestimated. Thus, it may prove difficult to diagnose and localize insulinoma using conventional hormonal studies alone. Furthermore, in our case, the patient’s fasting IRI levels were not elevated sufficiently to definitively diagnose insulinoma.

After surgery, 75g OGTT showed impaired glucose tolerance (IGT) pattern, with hypersecretion and prolongation of insulin before surgery. This may be due to: 1) insufficiency of recovery of β cell function which was suppressed by insulinoma, 2) insulin resistance due to obesity as a result of glucose administration for prevention of hypoglycemia, 3) diabetogenic state, concerning of her family history.

It is well known that secretin stimulates β cells to release insulin. However, it is not known whether secretin stimulates insulin release in insulinoma cells. Imamura et al reported that the secretin test (sensitivity 75% and specificity 100%) was
Insulinoma Diagnostics

Figure 3. Summary of secretin test. Preoperatively, the IRI level showed almost no response to secretin. After the resection of insulinoma, residual normal β cell secreted insulin in response to secretin stimulation. The results of Imamura et al (5) and those of ours were coincident in this respect. It is assumed that the peak IRI level of postoperative patients might reach that of healthy volunteers as normal β cell function recovers.

useful for differential diagnosis of insulinoma and β cell hyperplasia (5). Figure 3 summarizes the results of the secretin tests used by both Imamura et al and ourselves. In our patient, after enucleation of the tumor, there was a normal insulin secretion in response to secretin. The peak value of IRI in postoperative patients returns to the same level as that of healthy subjects. The use of this test assumes that normal β cells release insulin when stimulated by secretin, while insulinoma cells do not respond in vivo or in vitro (5). The lack of response against secretin may represent that the secretin receptor in the β cells in the insulinoma-bearing pancreas are under down-regulation in the condition of insulin hypersecretion. After extirpation of the tumor, normal β cell function is recovered, as revealed by the secretin test. These findings indicate that the secretin test is useful for both the preoperative diagnosis of insulinoma and for the postoperative confirmation of total insulinoma resection. In addition, the secretin test can be repeated during the pre- and postoperative stage in a non-invasive manner.

Because preoperative localization of pathologic sources of hyperinsulinism is reported to fail in as many as 40–60% of cases, and because 10% of insulinomas are reported to be multiple and malignant (1), it is very important to carefully and accurately localize insulinoma prior to surgery. The noninvasive modalities of ultrasound, CT, and MRI often fail to demonstrate insulinomas smaller than 15 mm in diameter (6). SACI was developed by Imamura et al and Doppman et al in 1990 (2, 6) and is now considered a primary diagnostic tool for assessing the location and function of insulinoma, replacing the use of percutaneous transhepatic portal venous sampling (PTVS) (7–12). Compared with PTVS, SACI is less invasive and more sensitive (96.6% versus 87.1%). Currently, the best curative treatment for insulinoma is complete resection. Therefore, it is indispensable to perform SACI, which supplies both accurate localization and highly refined sensitivity before surgery (12, 13).

In conclusion, careful diagnosis and localization of insulinoma is best obtained using the secretin test followed by SACI. Furthermore, administering the secretin test after tumor resection is valuable in the determination of residual β cell function.

References