Insulinoma-associated Transient Hypothalamus–Pituitary–Adrenal Axis Impairment and Amelioration by Steroid Therapy and Surgical Intervention: A Case Report

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Insulinoma is the most common functional tumor among pancreatic islet cell tumors. This type of tumor is difficult to localize prior to surgery and can lead to serious hypoglycemia. This paper presents the case of a young female who suffered from insulinoma associated with transient hypothalamus–pituitary–adrenal axis impairment. To localize her insulinoma, we used two alternative testing methods, somatostatin receptor scintigraphy and selective arterial calcium stimulation with venous sampling, after a failure of conventional imaging methods. We treated her adrenal insufficiency and prevented serious hypoglycemia by giving her prednisolone. The impairment in her hypothalamus–pituitary–adrenal axis and her serious hypoglycemia recovered after excision of the tumor.

Key Words: hypothalamus–pituitary–adrenal axis impairment, insulinoma
(*Kaohsiung J Med Sci* 2007;23:526–30)

Islet cell tumors of the pancreas are a rare entity among pancreatic tumors. Among them, insulinoma is the most common type. Because insulinomas can often be cured by surgical resection, it is important to precisely locate the tumor prior to surgery. However, due to their small size at the time of presentation, it is often difficult to locate their exact position. This article presents the case of a female who was diagnosed with insulinoma associated with hypoglycemia unawareness and transient impairment of the hypothalamus–pituitary–adrenal (HPA) axis.

Case Presentation

A 24 year-old female was found unconscious and brought to our hospital. On physical examination, her blood pressure was 126/68 mmHg, heart rate was 104 beats per minute, and body temperature was 36.7°C. Laboratory tests were in the normal range (Table 1) except for plasma glucose level (16 mg/dL). After receiving glucose water infusion, she recovered consciousness.

Received: November 24, 2006 Accepted: January 12, 2007
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After admission, the patient experienced several hypoglycemic attacks, but complained of no discomfort. A fasting test was arranged, but was terminated shortly thereafter because of her serious hypoglycemia. At the time of hypoglycemia, laboratory data were as follows: plasma glucose, 37 mg/dL (normal range, 70–100 mg/dL); C-peptide, 5.0 ng/mL (normal range, 0.5–2 ng/mL); insulin, 15.3 μIU/mL (normal range, 8.3–22 μIU/mL); cortisol, 5.3 μg/dL (normal range, AM 5–25 μg/dL, PM ≤ 1/2 AM value). This laboratory data indicated two possibilities: insulinoma or adrenal insufficiency.

Suspecting insulinoma-associated hypoglycemia, we arranged abdominal ultrasonography, abdominal magnetic resonance imaging and angiography with the intention of localizing the tumor. However, these methods failed to locate the tumor. There was an approximately 20-day outpatient period before the next examination. We arranged somatostatin receptor scintigraphy (SRS) using ^{111}In-octreotide. From the SRS result, we found that the possible tumor location was at the pancreas tail. This was further supported by selective arterial calcium stimulation with venous sampling (ASVS) (Table 2).

Table 1. Patient's biochemistry data on arrival at hospital

White cell count	7.5 × 1,000/μL
Hemoglobin	14.2 g/dL
Platelets	279 × 1,000/μL
Serum sodium	142.2 mmol/L
Serum potassium	4.3 mmol/L
Serum chloride	107 mmol/L
Aspartate aminotransferase	35 IU/L
Alanine aminotransferase	22 IU/L
Blood urea nitrogen	8.1 mg/dL
Serum creatinine	0.5 mg/dL
Ammonia	82 μg/dL
Ca^{++}	4.00 mg%

During the examinations for tumor location, a low cortisol level led us to arrange a desmopressin (1-deamino-8D-arginine vasopressin, DDAVP) test to evaluate her HPA axis. Surprisingly, we found that there was an inadequate increment in adrenocorticotropic hormone (ACTH) and cortisol levels after she took the DDAVP test (Table 3). The results of the desmopressin test indicated adrenal insufficiency in our patient. Therefore, in order to ameliorate her adrenal insufficiency during her outpatient period, we prescribed prednisolone 10 mg twice a day, and no serious hypoglycemia event occurred during this period.

After identifying the tumor location, surgery was performed. The surgeon palpated a tumor mass about 1.0 cm in diameter in the distal pancreas tail, and performed a distal pancreatectomy. The pathologist reported a benign insulinoma and the patient was free from hypoglycemia after the operation. After 6 months, we rechecked her cortisol and ACTH levels (cortisol, 16.1 μg/dL; ACTH, 29.1 pg/mL) and found that the function of her HPA axis had normalized.

Discussion

The incidence of insulinoma is approximately one case per 250,000 patient-years [1]. Seldom is any institution worldwide faced with more than nine cases per

Table 3. Adrenocorticotropic hormone (ACTH) and cortisol levels after 1-deamino-8D-arginine vasopressin test

	Time (min)				
	0	15	30	45	60
ACTH (pg/mL)	<19	<19	<19	<19	<19
Cortisol (μg/dL)	4.8	4.2	5.0	4.8	12.3

Table 2. Insulin level after selective arterial calcium stimulation with venous sampling

	Time (s)					
	Baseline	20	40	60	90	120
Artery (μIU/mL)						
Gastroduodenal	33.0	35.7	43.3	43.4	50.1	50.8
Superior mesenteric	25.1	29.3	22.1	32.8	29.8	32.6
Splenic	45.4	>373.0	>373.0	>373.0	182.2	292.0
Proper hepatic	13.6	9.2	12.2	11.8	14.6	10.5

calendar year [2–5]. There is a slight predominance of female cases [6]. The average age at diagnosis is about 50. Insulinomas are usually solitary and are located in different parts of the pancreas with an equal frequency. They are typically benign tumors (80–90%) with high vascularity [3,5], and often < 15 mm [7] at the time of diagnosis. The development of clinical symptoms results from uncontrolled secretion of insulin. Because small insulinomas are frequently undetectable with conventional imaging methods, their diagnosis is a great challenge to clinicians.

In this case, we chose abdominal ultrasonography and magnetic resonance imaging as our examination tools. However, although some reports have shown high detection rates of pancreas islet tumors using these methods [8,9], both of these failed in our case. From previous literature, we know that blind distal pancreatectomy is not an advisable procedure for occult insulinoma [10]. Therefore, alternative methods were necessary to locate the tumor. Insulinomas can be stimulated to secrete insulin following calcium infusion [11]. Selective ASVS has become an important method for preoperative assessment. Calcium gluconate (0.025 mmol Ca^{++}/kg) was injected into each selectively catheterized artery and blood samples were drawn from the right hepatic vein. According to the findings of Doppman et al [12], more than a two-fold rise in insulin levels within 30–120 seconds after the injection is required to localize the insulinoma. Sensitivities of 55–76% for detecting insulin-secreting tumors by ASVS are described in the literature [13]. Recently, functional imaging with SRS has added a further tool for the evaluation and detection of pancreatic neuroendocrine tumors (NET), based on the characteristic expression of human somatostatin receptor subtype 2 (hSSTR-2) [14]. In one study, 28% of patients were found to have previously unknown lesions using SRS [15]. Moreover, in some studies, SRS may alter the stage in 24% of patients and surgical strategy in 25% of patients. Although some insulinomas lack hSSTR-2, the sensitivity of SRS for detecting them still reaches 60%. As well as being an imaging tool, somatostatin analogues can also be used in the treatment of insulinomas.

Hypoglycemia unawareness, which was also found in this patient, has been largely discussed in type 1 and advanced type 2 diabetic patients. It is believed to be related to hypoglycemia-associated autonomic failure (HAAF) [16]. It has been proposed that elevated cortisol is responsible for HAAF [17–19]; however, this point of view has not been proven by subsequent studies [20,21]. Despite the role of cortisol in HAAF, our patient's cortisol and ACTH levels were low when hypoglycemic. Thus, we further proved the impairment of the HPA axis by using the DDAVP test. DDAVP is a companion regulator of corticotropin-releasing hormone in the control of ACTH synthesis, and the response rate is approximately 50–60% in normal healthy subjects [22]. After confirming the possibility of adrenal insufficiency, we prevented serious hypoglycemia by using prednisolone. Except for transient impairment of the HPA response before operation, our case showed similar findings to a case reported in another article [23], that is, increased levels of ACTH and cortisol after surgery. To the best of our knowledge, this impairment has never been illustrated in previous literature, and it may be related to the prolonged frequency of hypoglycemic episodes. However, the underlying mechanism remains unclear.

Like many other cases, we successfully identified the location of insulinoma using ASVS. However, this approach is still invasive and includes some unavoidable and troublesome complications. It is suggested that clinicians use SRS as a preoperative localization method since it is noninvasive and nearly as sensitive as ASVS.

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胰島素腫瘤合併暫時性下視丘—腦下垂體 — 腎上腺軸缺損且經由類固醇和手術治療緩解 — 一位成人病例報告

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胰島素細胞腫瘤在胰島細胞腫瘤中是最常見的功能性腫瘤。它會造成嚴重的低血糖而且通常很難在術前被定位出來。這病例報告是一年輕女性的胰島素細胞腫瘤合併暫時性下視丘—腦下垂體—腎上腺軸缺損。在經由傳統的影像學檢查失敗之後，我們成功的使用體泌素接受體閃爍攝影 (**somatostatin receptor scintigraphy**) 和選擇性動脈刺激、肝靜脈血液採樣術 (**selective arterial calcium stimulation and venous sampling**) 方法將腫瘤定位出來。此外也成功的使用 **prednisolone** 治療腎上腺功能不足與預防嚴重的低血糖。而她的下視丘—腦下垂體—腎上腺軸缺損與嚴重的低血糖在切除腫瘤之後就回復了。

關鍵詞：下視丘—腦下垂體—腎上腺軸缺損，胰島素細胞腫瘤

(高雄醫誌 **2007;23:526－30**)

收文日期：**95** 年 **11** 月 **24** 日

接受刊載：**96** 年 **1** 月 **12** 日

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