DOI: 10.25179/tjem.2017-56483
Turk J Endocrinol Metab 2017;21:85-88

The Experience from Ten Insulinoma Cases

Bir Seri İnsülinoma Olgusu: On Hastadaki Deneyimimiz

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Abstract

Introduction: Insulinoma is a rare, pancreatic functional neuroendocrine tumor, characterized by endogenous hyperinsulinemia, fasting hypoglycemia, and neuroglycopenic symptoms. It is diagnosed by a 72-h-fasting test, followed by localization studies. The common treatment option is the surgical excision. We hereby aim to discuss our clinical experience related to the patients of insulinoma.

Material and Method: A retrospective analysis was done on the history of the patients, who were hospitalized to our clinic due to hypoglycemia and biochemically detected insulinoma (glucose <55 mg/dL, whereas insulin > 3 µU/mL and C-peptide >0.6 ng/mL), between June 2007 and May 2015.

Findings: The average age of the patients was 52,6 and ranged from 18 to 85 years. Five patients were men and five were women. All of the patients presented with fasting hypoglycemia. In one patient, the tumor was detected by DOTATATE scintigraphy. Seven patients underwent surgery and were cured. One patient demonstrated metastasis. The tumor could not be localized by ultrasound, CT, and MRI in two patients, and therefore, they were subjected to surgery after localizing the tumor by advanced imaging methods.

Discussion: In patients with fasting hypoglycemia and neuroglycopenia, along with Whipple's triad, insulinoma should mainly be considered and a 72-h-fasting test should be conducted for diagnosis. The localization studies should be performed if the results are < 55 mg/dL for blood glucose, >3 µU/mL for insulin and > 0.6 ng/mL for C-peptide in blood sampled during the appearance of symptoms. We found that the triphasic thin slice CT, with multi-detector, was very useful for tumor localization in the test patients.

Keywords: Insulinoma; hypoglycemia; triphasic CT

Özet

Amaç: İnsülinoma, nadir görülen endojen hiperinsülinemi, açlık hipoglisemisi ve nörolojik bulgular ile seyreden pankreasın fonksiyonal nöroendokrin tümörüdür. Tanısı için 72 saatlik açlık testi uygulanmakta, sonrasında daha bölgesel çalışmalar yapılabilmektedir. Cerrahi eksizyon tedavi amaçlı uygulanabilmektedir. Bu çalışmada, insülinomalı 10 hastadaki deneyimlerimizin paylaşılması amaçlanmıştır.

Gereç ve Yöntem: Hasta dosyaları üzerinden retrospektif bir analiz gerçekleştirilmiştir. Çalışmada, Haziran 2007-Mayıs 2015 tarihleri arasında kliniğimize yatışı yapılmış, hipoglisemili ve biyokimyasal olarak yakalanmış insülinomalı (glukoz <55 mg/dL, insülin değeri >3µU/mL ve C-peptit >0,6 ng/mL) hastalar incelenmiştir.

Bulgular: Hastaların yaş aralığı 18-85 yıl idi. Ortalama yaşları 52 yıl olan hastalardan beşi erkek, geri kalanı kadındı. Tüm hastalarda açlık hipoglisemisi mevcut idi. Bir hastada, tümör DOTATATE sintigrafi ile saptandı. Yedi hastaya cerrahi tedavi uygulandı. Bir hastada metastaz izlendi. Başka merkezlerde ileri görüntüleme yöntemleri ile tümör tanısı aldıktan sonra cerrahi yapılan iki hastada ultrason, bilgisayarlı tomografi (BT) ve manyetik rezonans görüntüleme ile bir tümör saptanmamıştır.

Tartışma: Açlık hipoglisemisi ve nöroglikopeni ile tıbbi merkeze başvuran hastalarda, "Whipple" triadı da var ise insülinoma akla gelmeli ve tanı için 72 saatlik açlık testi uygulanmalıdır. Hastanın bulguları ortaya çıktığında kan glukozu <55 mg/dL, insülin değeri >3µU/mL ve C-peptit düzeyi >0,6 ng/mL ise lokalizasyon araştırmaları yapılmalıdır. Çok detektörlü üç fazlı ince dilimli BT'nin hastalarımızda tümör lokalizasyonunda çok faydalı olduğu görülmüştür.

Anahtar kelimeler: İnsülinoma; hipoglisemi; trifazik BT

Introduction

Insulinoma is the most common functional neuroendocrine pancreatic tumor, characterized by endogenous hyperinsulinemia, fasting hypoglycemia and neuroglycopenic symptoms with a probability of about four cases per million annually. It is more prevalent in women than the men and usually develops in people between 40 and 60 years of age (1,2). Insulinoma is generally sporadic, benign and solitary. Multiple localization and early onset of the disease occurs in multiple endocrine neoplasia type-1 (MEN1) syndrome. The estimates of the frequency of malign insulinomas

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may go up to 30% including elderly patients, multiplicity, and MEN1 syndrome equally (3). In particular, an inappropriate release of higher insulin levels independent of fasting glucose leads to the suppression of hepatic glucose output and results in fasting hypoglycemia. Sometimes, it may progress along with fasting as well as postprandial or rarely with only postprandial hypoglycemia. Due to the neuroglycopenic symptoms, some patients may erroneously be diagnosed with epilepsy or psychosis (4). The average tumor size is usually less than 2 cm; however, for tumors larger than 5 cm, malignity is frequent (5). Biochemical diagnosis is done by following a 72-h-fasting test. Nearly all patients would become hypoglycemic within first 48 h. Insulinoma can be suspected if the followings exist: Whipple's triad-glucose <55 mg/dL, hypoglycemia symptoms, improved symptoms with sugar intake, insulin >3 µU/mL and C-peptide >0.6 ng/mL (6). After biochemical diagnosis, abdominal ultrasonography (USG) may be conducted for the initial localization, and thereafter computed tomography (CT) or magnetic resonance imaging (MRI) should be performed for a more sensitive and accurate localization.

The insulinoma is treated by surgical excision. For malign tumors that are close to ductus localized in the pancreas, pancreatoduodenectomy is carried out, while for single small tumors, enucleation is directed and for large multifocal tumors at corpus and pancreatic tail, a distal pancreatectomy is performed (7). In addition, endoscopic USG, as well as hepatic venous sampling, may also be used, along with selective arterial calcium stimulation test. Intra-operative USG and palpation are performed for the tumors which fail to be localized before surgery. The neuroendocrine tumors cause overexpression of somatostatin receptors on the surface of tumors. Among the somatostatin receptor-based imaging methods in nuclear medicine, Gallium-68 DOTA draws attention as a promising novel model for localization (8). The present report is aimed to discuss our experiences on the diagnosis and treatment of insulinoma in the test patients.

Method

A retrospective analysis was conducted using the records of the patients hospitalized to our clinic due to hypoglycemia and biochemically diagnosed insulinoma (glucose <55 mg/dL, whereas insulin >3 µU/mL and C-peptide >0.6 ng/mL) between June 2007 and May 2015. The demographic characteristics, results of the 72-h-fasting test, as well as screening and pathological diagnosis from each patient record, were critically examined. The blood samples were taken for glucose levels every six hours at 60 mg/dL and every hour at ≤60 mg/dL, as well as for simultaneous levels of insulin, glucose, and C-peptide during symptomatic periods. The glucose <55 mg/dL, insulin and C-peptide levels were examined. Pancreatic images were obtained as triphasic 3-mm slices from the patients presenting insulinoma biochemically, using CT (Brillance 64 Philips) with 64 detectors at spiral mode. The patients who were not observed to carry any mass (tumor) by CT were subjected to MRI. In a patient where MRI failed to detect the tumor, gallium-68 DOTATATE was conducted. The patients were followed up with 10% dextrose infusion and blood sugar levels on an hourly basis before and during the surgery. After surgery, only the blood sugar levels were followed without dextrose infusion. Glucose levels were examined during the follow-up at the outpatient clinic after the surgery, on a monthly basis.

Findings

Of the total ten patients, five were men and five were women. The mean age of the diagnosis in our patients was 52 years, ranging from 18 to 85 years. All of the patients presented with fasting hypoglycemia. Only three patients had both fasting and postprandial hypoglycemia. One 18–year-old patient was followed up under psychosis diagnosis for three years because of incoherent behaviors during hypoglycemia. After a surgical operation, the symptoms of the patient were improved. All of our patients demonstrated hypoglycemia with neuroglycopenic symptoms within the first 12 h after the onset of fasting test. Due to the severe irritability and loss of consciousness, a 60-year-old male patient was found to have hypoglycemia. This patient had only neuroglycopenic symptoms, without any sympathoadrenergic signs during the hypoglycemic episode. All the patients underwent an abdominal triphasic CT scan with resultant mass observed in seven patients; however, in other three patients, no mass was found despite using MRI. In one patient, a mass was found by DOTATATE scintigraphy. The two patients who failed to localization studies were referred to an advanced center in order to perform endoscopic USG as well as surgery. All of the patients were examined for MEN-1 syndrome; however, none of them sustained MEN-1 syndrome. One of the patients had liver metastasis with a remarkable tumor of 9 3 cm in the pancreas. This patient could not be operated due to vascular invasion; therefore, he was followed for 15 months using oral diazoxide, verapamil, and monthly parenteral somatostatin and diet therapy. In the patients having mass, tumors were typically located at the pancreatic body. The ratio of insulin/glucose was found to be >0.3 during hypoglycemia in all the patients. In an 85-year-old male patient and a 56-year-old female patient, the insulin levels were 1000 µU/mL during hypoglycemia, which is the upper threshold limit. The levels of C-peptide were 17.64 ng/mL and 36.22 ng/mL, respectively. None of our patients used sulfonylurea. The ketone levels were found negative in the urine during a fasting test and randomly in all patients. They were administered a 10% dextrose infusion starting from the fasting period to the completion of surgery. In the post-operation period also, their glucose levels were monitored. None of the patients were found to have hypoglycemia after the surgery. In a 49-year-old female patient, the pancreatic fistula was developed after enucleation of the mass, and her condition was improved by somatostatin therapy. In another 56-year-old female patient, the mass was found at the head of the pancreas and uncinate process; therefore, she received the Whipple operation. However, she died post surgery due to acute renal failure and sepsis. Patient characteristics are summarized in Table 1.

Discussion

Insulinoma is a functional pancreatic tumor most frequently seen among adults, and the most common cause of endogenous hyperinsulinemic hypoglycemia, with an incidence of one in 250,000

Table 1. Demographic and laboratory features of the patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Mean
Age	55	65	18	18	60	61	49	59	85	56	52.6
Gender	F	F	M	M	M	M	F	F	M	F	E=F
Glucose (mg/dL)	36	33	28	52	27	29	44	53	42	32	37.6
Insulin (µU/mL)	11.43	15.76	94	30.84	28.12	22.53	22.31	37.08	1000	1000	226.2
C-peptide (ng/mL)	2.32	4.32	4.59	3.96	3.02	6.81	3.06	4.14	17.64	36.22	8.6
Insulin/glucose ratio	0.31	0.47	1.62	0.56	1.02	0.77	0.50	0.69	23.80	31.25	6.09
Neuroglycopenia	Exist	Exist	Exist	Exist	Exist	Exist	Exist	Exist	Exist	Exist	
Postprandial hypoglycemia	None	None	None	None	None	Exist	None	None	Exist	Exist	
Tumor size (mm)	9.5X6	30X22	18X12	12X15	?	91X38	26X21	16X11	?	15X12	>20
Localization/Imaging	Body-tail/DOTATATE	Body/CT	Body/CT	Head/CT	?	Body/CT	Body/CT	Body/CT	?	Head/CT	
Metastasis	None	None	None	None	None	Exist-L	None	None	None	None	
MEN 1 syndrome	None	None	None	None	None	None	None	None	None	None	
The onset of symptoms at fasting test	12th h	8th h	8th h	7th h	9th h	4th h	10th h	6th h	3rd h	2nd h	6.9
HbA1C	4.5	5.8	5.6	4.9	4.6	5.3	5.1	5.8	6.6	4.8	5.3
The type of operation	P1	P1	P1	E	?	inoperable	E	P1	?	Whipple	
Operative complications	None	None	None	None	None	inoperable	Fistula	None	None	ARF-Sepsis Exitus	
The length of follow-up (month)	1	51	96	49	15	54	2	1	3	1	27.4

F: Female; M: Male; CT: Computerize Tomography; P1: Distalpancreatectomy; E: Enucleation; L: Liver; ARF: Acute renal failure: The patients unable to reach their findings.

people. It usually appears in the fifties of a person. The average age of the test patients at diagnosis was 52 years (between 18 and 85 years). Insulinoma is more common in women than men (1,9). In our study, there were five women and five men. Generally, insulinoma is presented with fasting hypoglycemia and can suspectedly be diagnosed with hyperinsulinemic hypoglycemia. Some patients may demonstrate both fasting and postprandial hypoglycemia while others may have only postprandial hypoglycemia (10). All of our patients showed fasting hypoglycemia. However, three patients had both fasting and postprandial hypoglycemia.

Insulinoma is characterized by adrenergic and neuroglycopenic symptoms. Neuroglycopenic symptoms are related to the insufficient delivery of glucose to the brain. Hypoglycemia mostly occurs early in the morning, during sleep and after physical exercise. Patients may put on weight due to increased intake of nutrition resulting from hypoglycemia (10). All of our patients had neuroglycopenic symptoms, and nine patients were obese (BMI >30 kg/m^2), whereas one patient was cachectic.

After biochemical diagnosis, it is imperative to localize the insulinoma. The baseline imaging method is trans-abdominal USG. Triphasic abdominal CT stands as the most effective non-invasive imaging method. When CT imaging fails to show an adenoma MRI can be used. In case of non-localization of any mass by means of USG, CT, and MRI, endoscopic USG and invasive procedures may be performed. Coupling endoscopic USG with thin-sliced multidetector tomography would probably yield 100% accurate localization (11). Recently, gallium-68 DOTA scintigraphy has also been used for localization due to the fact that neuroendocrine tumors express somatostatin. Nearly half of the patients with insulinoma express type II somatostatin receptor (12). Tumors were localized in seven patients by the means of triphasic CT. In one patient, when adenoma could not be localized with CT and MRI, DOTATATE scintigraphy successfully localized the adenoma. In two patients, the tumors could not be localized by any of these means; therefore, they were referred to an advanced medical center for endoscopic and intra-operative ultrasonography.

Each of the eight patients with the localized tumors had a single-focal tumor, while the other two patients had double-focal tumors. Almost all insulinomas reported in the literature so far were localized within the pancreas (13). Likewise, in all of our patients, the adenomas were also localized in the pancreas.

The primary treatment of insulinoma is surgical removal of the adenoma. Surgical options include enucleation (if tumors can be excised), pancreatoduodenectomy (if any malign insulinoma and ductal invasion exist) and distal pancreatectomy (if a large and multifocal tumor exists in the tail or body). It is not recommended to perform a blind pancreatectomy (14). Patients were followed with 10% dextrose infusion during operation and blood sugar levels were checked hourly at the perioperative period. After the completion of surgery, blood sugar levels were monitored for a while.

In conclusion, if insulinoma is left untreated, it may become a life threatening disorder, therefore, it is important to diagnose and treat it properly. The patients with neuroglycopenic symptoms should be well informed about it. Triphasic abdominal CT may be used as the first step for localization. If radiological imaging fails, gallium–68 DOTATATE scintigraphy may be used.

Author Contributions

Concept: Alpaslan Kemal Tuzcu, Design: Faruk Kilinç, Data Collection or Processing: Zafer Pekkolay, Analysis or Interpretation: Mazhar Müslüm Tuna, Literature Search: Hi kmet Soylu, Writing: Zafer Pekkolay.

Conflict of Interest: No conflict of interest was declared by the authors

Financial Disclosure: The authors declared that this study received no financial support.

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