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Evaluation of the Clinical Characteristics, Diagnostic Methods, and Long-term Outcomes of Patients with Insulinoma

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ABSTRACT

Introduction: Insulinoma is a rare disease, however the most common cause of hypoglycemia due to excess insulin secretion. Diagnosis and localization can be challenging. This study evaluated the clinical features, diagnostic workup, management, and outcomes of patients with insulinoma.

Methods: The records of 13 patients with insulinoma who were followed up at İstanbul University, İstanbul Faculty of Medicine were retrospectively reviewed.

Results: The mean age of the 13 patients (female/male: 11/2) was 43.9±12.5 years at diagnosis. The mean tumor diameter was 14.3±6.7 mm and localized at the head in 30.8%, at the tail and/or body in 61.6%, and at both the head and body in 7.6% of patients. The tumor was correctly localized by magnetic resonance imaging in 10/13 patients, ^{68}Ga DOTATATE positron emission tomography/computed tomography in 4/8, endoscopic ultrasound in 3/7, and selective arterial calcium stimulation in 4/4 patients. Eleven patients were operated. Distal pancreatectomy was performed in 4 patients, distal pancreatectomy plus splenectomy in 3, and enucleation in 4 of the patients. The median follow-up duration was 4 years. In 8 patients, cure was achieved with surgery alone. Somatostatin receptor analog (SSRA) treatment was initiated in 2 cases and one of whom developed lymph node metastasis 2.5 years after surgery under SSRA treatment and she was reoperated. These patients had stable disease at the last visit.

Conclusion: Insulinomas are usually small tumors, but they can cause severe symptoms. A multidisciplinary approach is required for diagnosis and treatment. In some patients, different imaging modalities may be necessary for tumor localization.

Keywords: Insulinoma, pancreatic neuroendocrine tumor, hyperinsulinemic hypoglycemia

Introduction

Insulinoma is the most common functioning pancreatic neuroendocrine tumor (PNET) and is a rare disease with an incidence of 0.7-4 cases/million/year (1-4). Most insulinomas are sporadic tumors, but they can also be associated with hereditary syndromes, such as multiple endocrine neoplasia type 1 (MEN1), tuberous sclerosis complex, and neurofibromatosis type 1. More than 90% of insulinomas are benign, approximately 10% are multiple, and 5-10% occur in association with MEN1 syndrome. The risk of recurrence is higher in patients with MEN1 (2,5,6). Tumors originate from the beta cells of the pancreas and are characterized by increased insulin secretion, resulting in hypoglycemia. Hypoglycemia leads to autonomic symptoms, such as tremors, palpitations, diaphoresis, and hunger, as well as neuroglycopenia symptoms, such as confusion, cognitive impairments, visual changes, unusual behavior, memory loss, seizure, and impaired consciousness. Most patients with insulinoma present with Whipple's triad, which includes symptoms of hypoglycemia, documented low plasma glucose levels during symptoms, and symptom relief after carbohydrate ingestion. The diagnosis of insulinoma is delayed because of non-specific symptoms, and some patients are misdiagnosed as having neurological or psychiatric disorders (7).

Insulinoma is characterized by fasting hypoglycemia with inappropriately high insulin and C-peptide levels (hyperinsulinemic hypoglycemia). The diagnostic criteria at the time of symptomatic hypoglycemia (usually glucose level <45 mg/dL) are as follows: C-peptide level >0.6 ng/mL, insulin >3 µU/mL, and beta-hydroxybutyrate <2.7 mmol/L. However, some patients may present with postprandial hypoglycemia. Provocative tests are usually needed for diagnosis; a 72 h fasting test is recommended

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in patients with fasting hypoglycemia (5,8). The differential diagnosis of hyperinsulinemic hypoglycemia includes postbariatric surgery hypoglycemia, nesidioblastosis, autoimmune hypoglycemia, medications, and factitious hypoglycemia. Therefore, a detailed history, physical examination, and laboratory tests are important to determine the etiology (5).

The tumor is located in the pancreas in almost all cases. Non-invasive imaging procedures for tumor localization include computed tomography (CT), magnetic resonance imaging (MRI), ^{68}Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography (^{68}Ga DOTATATE PET/CT), and fluorine-18-L-dihydroxyphenylalanine PET (18F-DOPA PET). Another non-invasive functional imaging method for benign insulinoma that is not detected by CT/MR is ^{68}Ga-DOTA-exendin-4 PET/CT. GLP-1 receptors are overexpressed in benign insulinoma; thus, exendin-4 functional imaging is more sensitive (9,10). Invasive procedures include endoscopic ultrasound (EUS) and selective arterial calcium stimulation testing (SACST). EUS can detect small lesions that cannot be localized by non-invasive procedures (11,12).

Treatment options include surgery, non-surgical invasive procedures, and medical therapy. Surgical procedures include tumor removal by enucleation, distal pancreatectomy, and Whipple's operation. EUS-guided radiofrequency ablation is another treatment option for selected patients with localized insulinoma. Diazoxide, calcium channel blockers, and somatostatin receptor ligands are used to inhibit insulin secretion and control symptoms. Liver metastases can be resected or treated by cryoablation, chemoembolization, radioembolization, radiofrequency ablation, and brachytherapy. The treatment of inoperable or more aggressive insulinoma includes debulking surgery, SSRL therapy, everolimus, tyrosine kinase inhibitors, cytotoxic chemotherapy, and peptide receptor radionuclide therapy (5,13,14).

This study aimed to evaluate the clinical characteristics, diagnostic workup, management, and outcomes of patients with insulinoma.

Methods

This retrospective study included patients diagnosed with insulinoma who were followed up at the Endocrinology and Metabolic Diseases Clinic of İstanbul University, İstanbul Faculty of Medicine between 1986 and 2024. Demographic and clinical characteristics, laboratory results, diagnosis workup, treatment modalities, and treatment outcomes were obtained from the patients' medical records. Cure was defined as the absence of symptoms for at least six months after surgery.

The Ethics Committee of İstanbul University, İstanbul Faculty of Medicine, approved the study protocol (approval number: 02, date: 26/01/2024). Informed consent was not obtained because of the retrospective study design.

Statistical Analysis

Statistical analyses were performed using SPSS software (version: 21.0). Categorical variables were presented as frequency and percentage of occurrence, whereas numerical variables were presented as median, mean, and standard deviation. The Spearman's test was used for correlation analysis, A p-value of <0.05 was considered statistically significant.

Result

A total of 13 patients with insulinoma were included in this study. There were 11 women (84.6%) and 2 men (15.4%), and the female-to-male ratio were 5.5:1. The mean age at diagnosis was 43.9±12.5 years (median 39, range 28 to 73). The most common symptoms at presentation were confusion (5/13), tremors (4/13), dizziness (4/13), and diaphoresis (3/13). The other symptoms were syncope (2/13), poor memory (2/13), numbness in the hands and feet (2/13), blurred vision (1/13), fatigue (1/13), seizure (1/13), weight gain (1/13), and nightmare (1/13). One patient was misdiagnosed with narcolepsy, and another patient was followed up for a long time with the diagnosis of epilepsy. The median time from initial symptoms to diagnosis was 36 months.

The laboratory results of the patients at the time of admission were as follows: median glucose level, 68 mg/dL (range, 45 to 82), median insulin level 32 µU/mL (range, 5.8 to 201), median C-peptide level, 4.1 ng/mL (range, 1.5 to 15). Symptomatic hypoglycemia developed spontaneously in 6 patients and was detected by a 72-hour fasting test in 7 patients. Blood samples were taken at that time, and the results were as follows: median glucose level, 34 mg/dL (range, 20 to 49), median insulin level 16 µU/mL (range, 3.2 to 277), median C-peptide level, 3.2 ng/mL (range, 1.6 to 14.6). During the 72-hour fasting test, the median time to development of hypoglycemia was 18 hours (2 patients developed within the first 12 hours, 4 patients between 12-24 hours, and 1 patient after 27 hours). Six patients whose cortisol levels were not increased during hypoglycemia were found to have a sufficient cortisol response to the synthetic adrenocorticotrophic hormone stimulation test. HbA1c value of 7 patients was available and the median HbA1c was 4.7%.

One patient had a history of MEN-1-related disease. She had undergone surgery for hyperparathyroidism and Cushing's disease and had a non-functioning adrenal adenoma. Next Generation Sequencing was performed in this case, which revealed a pathogenic mutation in the *Menin* gene (*c.19C>T, p.Gln**).

The diagnostic methods used for tumor localization were as follows: MRI in all patients, ^{68}Ga DOTATATE PET/CT in 8, EUS in 7, and SACST in 4 patients (Figure 1). The tumor was correctly localized on MRI in 10 patients and on SACST in the remaining 3 patients (Table 1). In 1 of these 3 patients, the results of the ^{68}Ga DOTATATE PET/CT and SACST were consistent, while in the other 2 patients, the lesions were defined in different places. According to imaging studies, the mean tumor diameter was 17.7±8.9 mm (range, 9 to 35). The tumor was localized at the head in 4 patients (30.8%), at the tail/body in 4 (30.8%), at the tail in 2 (15.4%), at the body in 2 (15.4 %), and at both the head and body in 1 (7.6%) patient.

Eleven of the 13 patients underwent surgery. Distal pancreatectomy was performed in 4 patients, distal pancreatectomy and splenectomy in 3, and enucleation in 4 patients. Two patients were referred to the surgical department for operation (Whipple procedure for one and total pancreatectomy for the other patient) but they discontinued their follow-up.

According to pathological examination results, the mean tumor diameter was 14.3±6.7 mm (median 15 mm), in 8 patients tumor grade was available, and it revealed grades 1 in 2 patients, grade 2 in 5, and grade 3 in 1 patient. The median Ki67 index was 5% (range, 1 to 10) (Table 1).

The median follow-up duration from the first surgery to the last visit was 4 years (range, 2 months to 10 years) in the 11 patients who underwent surgery. In 8 patients, cure was achieved with surgery alone. Somatostatin receptor analog (SSRA) treatment was initiated in cases 8 and 12 after surgery but case 8 developed lymph node metastasis 2.5 years after the first surgery under SSRA treatment, and she was re-operated. These patients had stable disease at the last visit. One patient (case 9) could not be evaluated for remission due to the short postoperative follow-up period.

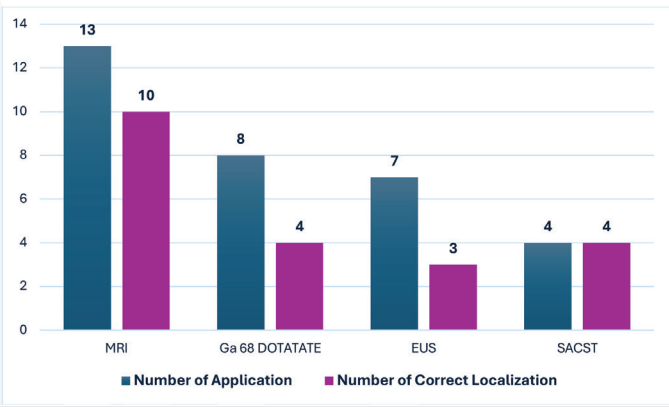

Figure 1. Success of invasive and non-invasive imaging methods in localizing the tumor
MRI: Magnetic Resonance Imaging, ^{68}Ga DOTATATE PET/CT: ^{68}Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography, EUS: Endoscopic Ultrasound, SACST: Selective Arterial Calcium Stimulation

Postoperative pancreatic fistula was observed in 2 patients after enucleation (2/4), and diabetes mellitus developed in two patients.

There was a correlation between insulin and C-peptide levels during fasting hypoglycemia and tumor size according to imaging methods (p=0.010; p=0.007, respectively). Furthermore, tumor size on pathological examination was positively correlated with fasting insulin levels and baseline insulin and C-peptide levels and negatively correlated with baseline glucose levels (p=0.010; p=0.022; p=0.003; p=0.008 respectively). Insulin and C-peptide levels during fasting hypoglycemia were positively correlated with baseline levels (Table 2).

Discussion

In this study, clinical manifestations, laboratory findings, diagnostic methods, localization, and treatment modalities of patients with insulinoma were reviewed and evaluated regarding the success of imaging modalities in the detection of tumors and treatment outcomes in a single center.

Placzkowski et al. (8) reported that the majority of patients with insulinoma were women (57%) and the median age was 50 years. Similarly, Mehrabi et al. (15) showed that insulinoma mostly occurred in the fifth decade of life, and the female-to-male ratio was 1.4:1 (59% female and 41% male). The mean age at diagnosis in our study was compatible with the results of the studies mentioned above. However, female predominance was more prominent, with a female-to-male ratio of 5.5:1 in this study.

Table 1. Characteristics of patients, localization methods, and treatment modalities

Patients	Gender	Age at diagnosis (years)	Duration of symptoms (months)	Diameter of tm (mm)	Localization MRI	Localization ^{68}Ga DOTATATE	Localization EUS	Localization SACST	Surgery procedure	Pathological examination grade/Ki67%
Case 1	F	35	12	11	Tail	-	-	-	DP	1%
Case 2	F	35	36	18	Head	-	-	-	E	4%
Case 3	F	50	36	22	Body	-	-	-	E	Grade 1/2%
Case 4	F	54	36	9	Head	Negative	Head	-	-	-
Case 5	M	44	120		Negative	Body	Negative	Distal pancreas	DP	Grade 2/5%
Case 6	F	30	36	10	Body/tail	Negative	Negative	-	DP	Grade 2/7%
Case 7	F	39	12	17	Head*	Head*	Head*	Distal pancreas	DP + S	Grade 2/7%
Case 8**	F	39	6	23	Body/tail	Tail	-	Distal pancreas	DP	Grade 1/1%
Case 9	F	73	180	30	Tail	Tail	-	-	DP + S	3%
Case 10	M	37	48	35	Head-body	-	-	-	-	-
Case 11	F	51	120	11	Head	Head	Head	-	E	Grade 2/5%
Case 12	F	55	18		Negative	Head*	Negative	Distal pancreas	DP + S	Grade 2/10%
Case 13	F	28	24	10	Head	-	Head	-	E	Grade 3/10%

Tm: Tumor, MRI: Magnetic resonance imaging, ^{68}Ga DOTATATE PET/CT: ^{68}Ga tetraazacyclododecanetetraacetic acid-DPhe1-Tyr3-octreotate positron emission tomography, EUS: Endoscopic ultrasound, SACST: Selective arterial calcium stimulation, DP: Distal pancreatectomy, DP + S: Distal pancreatectomy plus splenectomy, *: Suspected, **: Case 8 had multiple tumors associated with MEN-1

Table 2. Correlation between parameters associated with insulinoma

	During fasting hypoglycemia			Baseline		
	Insulin levels	C-peptide levels	Glucose levels	Insulin levels	C-peptide levels	Glucose levels
Insulin levels During fasting hypoglycemia,	-	**p<0.001 (CC: 0.988)**	p=0.672 (CC: -0.137)	**p<0.001 (CC: 0.924)**	**p<0.001 (CC:0.882)**	p=0.211 (CC: -0.389)
C-peptide levels during fasting hypoglycemia	**p<0.001 (CC: 0.988)**	-	p=0.973 (CC: -0.012)	**p<0.001 (CC: 0.952)**	**p=0.002 (CC: 0.883)**	p=0.382 (CC: -0.311)
Glucose levels During fasting hypoglycemia,	p=0.672 (CC: -0.137)	p=0.973 (CC: -0.012)	-	p=0.553 (CC: -0.213)	p=1.000 (CC: 0.001)	p=0.820 (CC: -0.074)
Tm diameter*	**p=0.010 (CC: 0.762)**	**p=0.007 (CC: 0.850)**	p=0.894 (CC: -0.049)	p=0.188 (CC: 0.518)	p=0.293 (CC: 0.395)	p=0.866 (CC: -0.061)
Tm diameter**	**p=0.010 (CC: 0.797)**	p=0.091 (CC: 0.635)	p=0.567 (CC: -0.221)	**p=0.022 (CC: 0.781)**	**p=0.003 (CC: 0.865)**	**p=0.008 (CC: -0.809)**
Age at diagnosis	p=0.470 (CC: 0.231)	p=0.213 (CC: 0.460)	p=0.648 (CC: -0.147)	p=0.590 (CC: 0.195)	p=0.246 (CC: 0.466)	p=0.110 (CC: -0.485)

Tm: Tumor, CC: Correlation coefficient, * Based on imaging modalities, **: According to pathological examination

The symptoms of insulinoma are non-specific. Therefore, the mean time from symptom onset to diagnosis may range from a few months to several decades. The mean delay between clinical manifestation and diagnosis was reported as 3.6±5.2 years in the study by Hirshberg et al. (16). In our study, the median duration of delay until diagnosis was 3 years, and it was 10 years for the patient with the longest diagnostic delay. A typical finding of insulinoma is fasting hypoglycemia. However, some patients with insulinoma present with hypoglycemia during the postprandial period. Placzkowski et al. (8) reported that 6% of patients presented with symptoms of postprandial hypoglycemia. In our study, hypoglycemia occurred during fasting in all patients.

Complete tumor resection provides remission in insulinoma. However, precise tumor localization is required for surgery. Mehrabi et al. (15) reported that the mean sensitivity of MRI was 57.7%. In our study, MRI was used to identify insulinoma in all patients, and in 10 of 13 patients, the tumor was correctly localized. In a study by Nockel et al. (17), they reported that the tumors were correctly localized in 17 out of 28 (61%) by MRI, and in 9 out of 10 (90%) by ^{68}Ga DOTATATE PET/CT (17). ^{68}Ga DOTATATE PET/CT is a sensitive method for detecting PNETs; however, its success in detecting insulinoma may be lower than that in other NETs because of the relatively lower SSTR expression of insulinoma (18). In our study, 8 patients underwent ^{68}Ga DOTATATE PET/CT imaging. The tumor could be localized in 4 of these 8 patients (50%). Sotoudehmanesh et al. (19) reported that the sensitivity of EUS for insulinoma detection was 92.6% for tumors located in the head of the pancreas, 78.9% for tumors located in the body, and 40.0% for tumors located in the tail. In our study, EUS was performed in seven patients. In 3 of them, the tumor was localized correctly. In the remaining 4 patients, the lesion was located in the distal pancreas and could not be detected by EUS.

In a study by Mehrabi et al. (15), it was shown that the mean tumor size was 16.7 mm (≤20 mm in 83.6% of patients), and the tumor originated from the head and neck in 43.3% of patients, from the tail in 30.9%, and from the body in 25.3%. Similarly, the mean tumor diameter was 14.3±6.7 mm in the study. However, consistent with the observation that beta cells are mostly found in the body and tail of the pancreas, the tumor primarily originated from the body and tail in our patients. Similarly, Sakurai et al. (20) reported that in 73% of patients, tumors originated from the distal pancreas.

Guidelines recommend a first-line surgical strategy for parenchyma-sparing pancreatic resection if technically feasible (5). Sakurai et al. (20) stated that distal pancreatectomy was performed in 32% of the patients, tumor enucleation in 22% patients, and distal pancreatectomy plus tumor enucleation in 8%. In the study of Mehrabi et al. (15), enucleation was the most commonly performed type of surgery (56%) (15). Because most insulinomas were localized in the body or tail of the pancreas, distal pancreatectomy was the most commonly selected procedure (7/11), followed by tumor enucleation (4/11) in our study.

Studies by Placzkowski et al. (8) and Mehrabi et al. (15) showed that 6% of insulinoma were associated with MEN-1. MEN-1 is associated with multiple tumors, a higher rate of malignancy, and recurrence (2). In our study, only 1 patient developed aggressive insulinoma (7.6%), which was associated with MEN-1 syndrome. Mehrabi et al. (15) reported mean cure and recurrence rates of 93% and 7.2% respectively. Recurrence was not observed in our study, and after excluding patients with short-term follow-up, the cure rate after surgery was 80% (8/10). Two patients underwent SSRA treatment and had stable disease (2/10) in our study cohort.

Study Limitations

The first limitation of our study was the small number of patients due to the low incidence of insulinoma. In addition, given that ^{68}Ga DOTATATE PET/CT was not performed in all patients, we could not compare the success of imaging methods in localizing the tumors.

Conclusion

Insulinomas are the most common cause of endogenous hyperinsulinemic hypoglycemia. Management and localization can be challenging despite teamwork. Parenchyma-sparing surgery is recommended for patients with localized insulinoma. Furthermore, in case of a history and/or symptoms associated with MEN 1 syndrome, the patient should be referred for genetic evaluation.

Ethics Committee Approval: The Ethics Committee of İstanbul University, İstanbul Faculty of Medicine, approved the study protocol (approval number: 02, date: 26/01/2024).

Informed Consent: Informed consent was not obtained because of the retrospective study design.

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