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Original Article

Evaluation of Insulinoma Cases Presented With Hyperinsulinemic Hypoglycemia: A Single-Centre Experience

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ABSTRACT

Background Insulinomas constituting the most common cause of endogenous hyperinsulinism-related hypoglycemia are neuroendocrine tumors originating from pancreatic beta cells. They are generally benign and solitary lesions. Although most cases are sporadic, multiple endocrine neoplasia (MEN) 1-related patients are also present.

Material and Methods Thirteen patients followed up in Bursa Uludag University Medical Faculty Endocrinology and Metabolic diseases clinic between the years 2012 and 2021 were retrospectively evaluated. Demographical, clinical, biochemical, radiological and histopathological data of the patients were assessed.

Results Eight of the patients were females, and five were males with an average age of 43±14.9 years. Ten of the patients had sporadic, and three had MEN1 syndrome-related insulinoma. During the prolonged fasting test, the patients had a mean lowest plasma glucose level of 36.4±6.2 mg/dL with a simultaneous mean insulin level of 11.3 (4.4-214.1) mIU/L and c-peptide level of 2.8 (0.46-12.8) mcg/L. In preoperative localization studies, a lesion was detected in 11 out of 13 (84.6%) patients with upper abdominal computed tomography and 6 out of 10 patients (60%) with magnetic resonance imaging. Six patients had grade 1, and 7 patients had grade 2 neuroendocrine tumor. The whole group's mean lesion diameter was 15 (11-48) mm. The mean patient follow-up duration was 30.5±23 months. Hypoglycemia recurred in none of the patients in the postoperative period, and only two patients (15.4%) developed postoperative diabetes mellitus.

Conclusions Preoperative localization rates in insulinomas increased due to non-invasive imaging methods and technological developments in recent years. This will probably cause earlier diagnosis and treatment, and pancreas preserving surgery option will be more available in most insulinoma cases.

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Introduction

Insulinomas are neuroendocrine tumors originating from pancreas beta cells. These tumors are known as the most common cause of endogenous hyperinsulinism-related hypoglycemia. The annual incidence of insulinomas is 0.4/100,000 individuals.[1] They are generally seen between the ages of 40 and 50 years. Insulinoma prevalence does not differ between the genders.[2] Benign and single lesions constitute 90% of the cases.[3] The presence of hypoglycemia, also known as the Whipple triad, is defined by the presence of sympathoadrenergic and/or neuroglycopenic symptoms of hypoglycemia and recovery of these symptoms through glucose intake define the main characteristic of insulinoma diagnosis.[2] Although hypoglycemia is mainly seen during fasting in insulinoma cases, it can also be seen following food intake.

Insulinoma can also be observed in 10-15% of patients diagnosed with multiple endocrine neoplasia type 1 (MEN1), although most insulinoma cases are sporadic.[4] Localizations of the lesions are tried to be detected through preoperative imaging studies in clinically and biochemically diagnosed insulinoma cases. Surgery is the primary curative option for lesions localizable through non-invasive and/or invasive methods. Different pharmacological treatment approaches can be applied in non-operable cases or required cases to control hypoglycemia until the surgery.[2] In this study, our objective was to discuss insulinoma diagnosis and treatment in light of the literature by presenting the demographical and clinicopathological characteristics of 13 insulinoma cases diagnosed and treated in our clinic.

Material and Methods

Study Population and Protocol

The study's consent was taken from Bursa Uludağ University Ethics Board. Thirteen patients hospitalized and examined in Bursa Uludağ University Endocrinology and Metabolism Diseases clinic due to hypoglycemia between January 1st 2012 and December 31st 2021 were included in the study. All patient data were attained retrospectively from the hospital record system. Patients who were clinically diagnosed with hyperinsulinism-related hypoglycemia had lesion localization provided through preoperative or intraoperative imaging and were histopathologically reported to have neuroendocrine tumors were included in the study. Patients whose diagnostic tests, surgical treatment and pathological evaluation were not performed in our centre were not included in the study.

If the measurement for diagnosis was impossible at the moment of spontaneous hypoglycemia, a 72-hour prolonged fasting test was started after the last meal and 1-2 hour routine capillary glucose measurements were made during the follow-ups. Plasma glucose, c peptide and insulin were measured in patients who developed hypoglycemia symptoms or were asymptomatic and had capillary glucose measurements detected below 70 mg/dL. Synchronous insulin level ≥3 mIU/L and c-peptide level ≥0.6 mcg/L with plasma glucose below 55 mg/dL were evaluated as the biochemical diagnosis for insulinoma. The test was ended with intramuscular or subcutaneous 1 mg glucagon injection in patients who were symptomatic and had plasma glucose value below 55 mg/dL or were asymptomatic with plasma glucose value below 45 mg/dL. Plasma glucose measurements were made in the 10th, 20th and 30th minutes following injection. Insulinoma was considered if plasma glucose had an increase over 25 mg/dL following glucagon application.

If required, a standard mixed meal test was performed following overnight fasting in patients with defined postprandial hypoglycemia symptoms. Samples were taken for glucose, insulin and c-peptide for five hours following 300 kcal (60% carbohydrate, 20% fat and 20% protein) food intake. Insulin and c-peptide values were evaluated during hypoglycemia.

Statistical Analysis

Sampling normality was evaluated through the Shapiro-Wilk test. Mean±standard deviation (SD) was used in normally distributed constant variables, and median (minimum-maximum values) was used for variables lacking normal distribution. Two independent variables were evaluated through student T or Mann-Whitney U tests. Kruskal-Wallis test was used in multiple variable conditions. $p<0.05$ was regarded as

statistically significant. SPSS (Statistical Package for the Social Sciences) 23 program was used for statistical analysis.

Results

Eight (61.5%) of the patients were female, and five (38.5%) were male. The average age of all patients was 43±14.9 years. The average age of females was significantly higher than males (51.7±9.9 years and 29.2±10.3 years respectively; p=0.002). Ten patients (7 female and 3 male) had sporadic, and three (1 female and 2 male) had familial insulinoma (MEN1). The average age was 30±12.3 years for patients with MEN1 syndrome and 47±13.8 years for sporadic patients. No significant difference was detected among them (p=0.06). Body mass index (BMI) was 36.9±7.7 kg/m^2 in females and 30.3 (26.7-40.6) kg/m^2 in males with no statistically significant difference among them (p=0.22).

Four females had hypertension, and 1 male had hypothyroidism as a comorbid disease. Nine patients had sympathoadrenergic symptoms or neuroglycopenic symptoms during the first admission. Four patients had no significant symptoms defined. Demographical and clinical characteristics of the patients during admission are shown in Table 1.

A 72-hour prolonged fasting test was made to investigate hypoglycemia etiology in eleven patients. Meantime between the start of the test and hypoglycemia detection was 7.09±7.66 hours in all patients and 9±8.79 hours in females and 2 (1-10) hours in males (p=0.25). Based on the prolonged fasting test, the plasma glucose of the patients was 36.4±6.2 mg/dl, insulin was 11.3 (4.4-214.1) mIU/L, and c-peptide was 2.8 (0.46-12.8) mcg/L (*Table 2*). Standard meal test was performed in two patients, including one male and one female, with postprandial hypoglycemia defined in anamnesis. Values for glucose and insulin were 19 and 28 mg/dL and 17.4 and 4 mIU/L, respectively.

In preoperative localization imaging, the pancreatic lesion was detected in 1 out of 6 patients whose ultrasonography (USG), in 11 out of 13 patients (84.6%) whose upper abdominal computed tomography (CT) and in 6 out of 10 patients (60%) whose upper abdominal magnetic resonance imaging (MRI) reports were available.

Table 1. Demographic and clinical patient characteristics.

	All patients	Female	Male	p value
Gender n (%)	13	8 (61.5%)	5 (38.5%)	
Age (years)	43±14.9	51.7±9.9	29.2±10.3	0.002
BMI (kg/m^2)	34.1±7.5	36.9±7.7	30.3 (26.7-40.6)	0.22
Symptoms				
Sympathoadrenergic (n)	9	7	2	
Neuroglycopenic (n)	9	5	4	
Comorbid diseases				
Hypertension (n)	4	4	-	
Hypothyroidism (n)	1	-	1	
MEN1 syndrome (n)	3	1	2	
SBP (mmHg)	137.1±16.8	134.5±11.7	140.8±23.3	0.55
DBP (mmHg)	86.4±11.7	86.8±11.3	85.8±13.5	0.88
Pulse (per min)	91.5±22.1	93.4±16.2	88.8±30.6	0.74

BMI: body mass index. SBP: Systolic blood pressure, DBP: diastolic blood pressure

Table 2. Prolonged fasting test evaluation.

	All patients	Female (n=7)	Male (n=4)	p value
Time to hypoglycemia (hours)	7.09±7.66	9±8.79	2 (1-10)	0.25
Plasma glucose (mg/dL)	36.4±6.2	31 (28-44)	38 (34-43)	0.44
Insulin (mIU/L)	11.3 (4.4 - 214.1)	7.3 (4.4-30.9)	15.6 (11.3-214.1)	0.08
C-peptide (mcg/L)	2.8 (0.46-12.8)	2.71 ± 2.15	3.35 (2.8-12.8)	0.18

Lesions detected in CT were in the head of the pancreas in five patients (45.5%), in the body of the pancreas in two patients (18.2%) and pancreatic tail in four (36.4%) patients. The number of patients with lesions detected at these locations in MRI was 3 (50%), 1 (16.7%) and 2 (33.3%), respectively. The maximum mean lesion diameter was 16.6±6.87 mm for all localizations, 20.6±7.23 mm for the head, 14.5 (13-16) mm for the body and 12.25 (7-20) mm for the tail in CT. Lesion dimensions were similar among all parts of the pancreas (p=0.25).

A calcium stimulation test was made in a total of three patients, including two patients with undetectable results in CT and one patient with suspicious localization in preoperative localization imaging. Patients were referred to surgery after determining the localization through this test.

All patients had surgery. Four patients (30.8%) had enucleation, three (23.1%) had partial distal pancreatectomy, five (38.5%) had Whipple procedure, and one (7.7%) had total pancreatectomy. Surgical reports showed that seven of the lesions were (53.8%) located in the pancreas head, one (7.7%) in the body, and four (30.8%) in the tail. No localization information was available in the surgical report of one patient.

Histopathologically, six of the patients had grade 1 neuroendocrine tumor (NET), and seven had grade 2 NET according to WHO 2017 classification. The mean diameter of the lesions was 15 (11-48) mm in the whole group and 16.25±4.74 mm in females, and 26.4±13.3 mm in males (p=0.07).

The mean patient follow-up duration was 30.5±23 months. Hypoglycemia recurred in none of the patients in the postoperative period, and diabetes mellitus was diagnosed only in two (15.4%) patients after surgery. None of the patients had recurrent lesions. One patient had liver metastasis during diagnosis and was cured through resection. It was observed that one patient used diazoxide and octreotide together, and one patient used only octreotide for hypoglycemia control in the preoperative period. None of the patients needed pharmacological treatment for hypoglycemia in the postoperative period.

Discussion

Demographical and clinicopathological characteristics of a total of 13 insulinoma cases, including 8 females and 5 males followed up in our clinic, were evaluated in our study. Diagnosis age was reported as 4-5th decades in the insulinoma cases in literature as in our patients.[5-7] Insulinoma can be seen earlier in familial MEN-1 cases. Younger diagnosis age in male patients in our study can be explained by the higher MEN-1 case rate in this group. Higher mean body mass index in our group compared to literature can be explained by the higher rate of female patients who have a more common rate of obesity, more prolonged hyperinsulinism exposure and ethical and/or cultural differences in our study group.[7] A significant difference was not detected when the patients' systolic and diastolic blood pressures were compared to literature.[8]

Based on 72-hour prolonged fasting tests made while investigating hypoglycemia etiology, nearly 2/3 of the patients became symptomatic or hypoglycemic in the first 24 hours of the test while most of the remaining patients became symptomatic or hypoglycemic in the first 48 hours.[2] All of our cases became symptomatic and

hypoglycemic in the first 24 hours. This situation can be related to the low number of our patients and their latter admission with the established clinical presentation to our hospital, a tertiary health centre.

In preoperative imaging studies performed after the clinical and biochemical provision of insulinoma diagnosis, localization success was provided at a rate of 84.6% through abdominal CT and 60% through MRI in our cohort. While lesion detection rates through MRI in literature were similar to our study, sensitivity through CT was detected lower.[6,9,10] Higher CT positivity rates in our study may be caused by the higher experience of our centre in CT evaluation or lesion diameters >1 cm during admission.

Other studies in the literature reported higher sensitivity rates for PET-CT compared to other conventional (such as CT, MRI) imaging methods. Our study could not provide a clear comparison on this subject as PET-CT result was available for only one patient.[6]

Insulinoma can be seen as a component of familial MEN-1. While a study detected the rate of patients diagnosed with MEN-1 as 6%, this rate was 23% in our patients.[11] This situation can be explained by the low number of our patients and the fact that our hospital is a tertiary centre.

Surgery is the curative treatment option for benign insulinomas.[2] Pancreas preserving surgery is recommended in these patients.[12] While the enucleation preference rate was approximately 60% in the surgical approach, the number of Whipple operations was relatively high in our cases.[13] This difference in the selection of surgical methods can be related to the admission of more severe cases as our hospital is a tertiary centre and the experience and approach of the surgeon.

An analysis in the literature reported that out of 25 patients with surgical and/or pathological reports available, 10 had tumors detected in the head of the pancreas, 4 in its body and 11 in its tail region.[14] While head and tail localization were similarly higher in our patients, body localization was interestingly lower. Although tumor sizes differed among the studies, they were similar to our study.[15]

Previous studies reported post-operative cure in nearly 90% of benign insulinomas in 10-20 year follow-up durations.[1] Hypoglycemia was not observed in any of the patients after surgery in an evaluation of 10 insulinoma cases published in our country.[14] Although the follow-up duration of our patients was shorter compared to the literature, cure rates were similarly relatively high. Diabetes mellitus formed in two of our patients (15.4%) in postoperative follow-ups, and this rate was somewhat higher than 2.2%, which was the rate in literature.[11] This high rate can be explained by Whipple and/or total pancreatectomy was made in a higher rate of our patients. Although recurrence rates of post-operative insulinoma were higher in MEN1 patients than the other patient group in the literature, recurrence has not yet been observed in our patients with MEN1 syndrome as the follow-up period was not long enough in our study.[1]

Conclusions

As a result, clinical and biochemical diagnosis approaches are essential in individuals with suspected insulinoma. Preoperative localization rates in insulinomas increase parallel to non-invasive imaging methods and technological developments in recent years. This will probably cause diagnosis and treatment to be provided earlier and the pancreas preserving surgery option to stand out more in most insulinoma cases. The low number of cases, short follow-up duration and lack of new imaging modalities in our centre were the weaknesses of our study. The strengths of our research are the application of all current approaches in our centre for all patients and the coordinated multidisciplinary approach of endocrinology, radiology, general surgery and pathology units.

Multi-centred studies with a high number of cases for a more detailed evaluation of the diagnoses, treatments and follow-ups of insulinomas will contribute significantly to literature in terms of medical and surgical approaches, diagnosis of these patients in a shorter period and application of effective imaging methods.

Acknowledgment

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Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the ethics committee of Uludag University (approved number: 2022-2/9).

This chapter does not contain any studies with animals performed by any of the authors.

Authors' Contribution

Study Conception: EA, CE; Study Design: CA, EE; Supervision: EH, OOG; Data Collection and/or Processing: FMS, SC; Statistical Analysis and/or Data Interpretation: EA, CE; Literature Review: EA; Manuscript Preparation: EA; and Critical Review: CE.

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