



## A 60-year experience in the treatment of pancreatic insulinoma in the Military Medical Academy, Belgrade, Serbia

Lečenje insulinoma pankreasa u Vojnomedicinskoj akademiji, Beograd:  
60-godišnje iskustvo

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### Abstract

**Background/Aim.** Insulinomas are rare benign tumors in the most cases and the most frequent endocrine tumors of the pancreas. A wide spectrum of clinical manifestations in patients with insulinoma is the reason for difficult recognition of the disease with a long period of time between the onset of symptoms and the diagnosis. Diagnostic procedures include Whipple's triad, 72-hour fast test and topographic assessment. The only curative therapy for patients with insulinoma is operative treatment. **Methods.** This retrospective study included 42 patients with diagnosis of insulinoma treated in our institution in a 60-year period. In all the patients a demographic and clinical data, types of biochemical methods for diagnosis, and diagnostic procedures for insulinoma localization were analyzed. Tumor size and localization, surgical procedures, postoperative complications and outcome were assessed. **Results.** A study included 42 patients, 29 women and 13 men. The median age at diagnosis was 43 years. Median time between the onset of symptoms and diagnosis was 3 years. The most common clinical symptoms and signs were disturbance of consciousness and abnormal behavior in 73%, confusion and convulsions in 61% of patients. The diagnosis of insulinoma was estimated by Whipple's

triad and 72-hour fast test in 14 patients. Determination of insulinoma localization was assessed by angiography in 16 (36%) of the patients, by ultrasound (US) in 3 of 16 (18.8%) patients, by abdominal computed tomography (CT) in 8 of 18 (44.5%) patients, and magnetic resonance imaging (MRI) in 2 of 8 (25%) patients. Insulinoma was found in 13 of 13 (100%) patients by arterial stimulation with venous sampling (ASVS) and in 13 of 14 (93%) patients by endoscopic ultrasound (EUS). Of the 42 patients, 38 (90.5%) underwent operative procedure. Minimal resection was performed in 28 (73.6%) of the patients [tumor enucleation in 27 (71%) and central pancreatectomy in one (2.6%) of the patients], and the major resection was performed in 9 (23.6%) of the operated patients [distal splenopancreatectomy in 8 (21%) and pancreaticoduodenectomy in one (2.6%) patient]. The overall mortality rate in postoperative period was 2.6% (one patient). **Conclusion.** A combination of ASVS and EUS as diagnostic procedures ensures high accuracy for preoperative determination of insulinoma localization. Minimal resection such as enucleation should be performed whenever it is possible.

**Key words:** insulinoma; diagnosis; digestive system surgical procedures; treatment outcome.

### Apstrakt

**Uvod/Cilj.** Insulinomi su retki, najčešće benigni tumori i najčešći endokrini tumori pankreasa. Širok spektar kliničkih manifestacija kod bolesnika sa insulinomom razlog je za otežano otkrivanje bolesti sa dugim periodom od početka simptoma do postavljanja dijagnoze. Dijagnoza se postavlja na osnovu Whipple-ove trijade, 72-časovnog testa gladi i morfoloških ispitivanja. Terapija koja može dovesti do potpunog izlječenja je hirurško uklanjanje tumora. **Metode.**

Retrospektivnom studijom obuhvaćeno je 42 bolesnika sa dijagnozom insulinoma, lečenih u našoj ustanovi u 60-godišnjem periodu. Kod svih bolesnika analizirane su demografske i kliničke karakteristike, načini postavljanja dijagnoze i dijagnostičke procedure za određivanje lokalizacije insulinoma. Procenjena je veličina tumora i lokalizacija, vrsta hirurške intervencije, postoperativne komplikacije i ishod lečenja. **Rezultati.** Studijom je obuhvaćeno 42 bolesnika, 29 žena i 13 muškaraca. Medijana starosti u vreme postavljanja dijagnoze bila je 43 godine. Medijana vremena

protektlog od početka simptoma do dijagnoze bila je tri godine. Najčešći klinički simptomi i znaci bili su poremećaji stanja svesti i ponašanja kod 73%, konfuzija i konvulzije kod 61% bolesnika. Dijagnoza insulinoma potvrđena je pomoću Whipple-ove trijade i 72-časovnog testa gladi kod 14 bolesnika. Lokalizacija insulinoma određena je angiografijom kod 16 (36%) bolesnika, ultrasonografijom (US) kod tri od 16 (18,8%) bolesnika, kompjuterizovanom tomografijom (KT) abdomena kod osam od 18 (44,5%) bolesnika i magnetnom rezonancijom (MR) kod dva od osam (25%) bolesnika. Insulinom je pronađen kod 13 od 13 (100%) bolesnika uz pomoć arterijske stimulacije sa venskim smplovanjem (ASVS) i kod 13 od 14 (93%) bolesnika pomoću endoskopske ultrasonografije (EUS). Od ukupno 42 bolesnika, 38 (90,5%) je operisano. Minimalna resekcija izvedena

je kod 28 (73,6%) bolesnika [enukleacija tumora kod 27 (71%) i centralna pankreatektomija kod jednog (2,6%) bolesnika] i velika resekcija samo kod devet (23,6%) operisanih bolesnika [distalna splenopankreatektomija kod osam (21%) bolesnika i duodenopankreatektomija kod jednog (2,6%) bolesnika]. Ukupna stopa smrtnosti u postoperativnom periodu bila je 2,6% (jedan bolesnik). **Zaključak.** Kombinovanje ASVS i EUS kao dijagnostičke procedure omogućava veliku tačnost u preoperativnom određivanju lokalizacije insulinoma. Minimalna hirurška resekcija, kao što je enukleacija, trebalo bi da se sprovodi kada je god moguće.

**Ključne reči:**  
**insulinom; dijagnoza; hirurgija digestivnog sistema, procedure; lečenje, ishod.**

## Introduction

Insulinoma is a tumor of the pancreas that is derived from beta cells of Langerhans islands. It is small, usually solitary tumor, which can be localized throughout the pancreas. Insulinoma is a benign tumor in 90% cases with the incidence of 1 to 4 per one milion humans per year<sup>1,2</sup>. It can appear as solitary sporadic tumor in patients without other diseases, but can be a part of multiple endocrine neoplasia type 1 (MEN 1), usually in a form of multiple tumor. The average age of its occurrence is 45 years for sporadic cases and 25 years for MEN 1<sup>1,3,4</sup>. Typical manifestations of insulinoma are the symptoms of hypoglycemia usually provoked by fasting or exercising<sup>5</sup>. A wide spectrum of clinical manifestations in patients with insulinoma is the reason for difficult recognition of disease with a long time interval between the onset of symptoms and the diagnosis. Insulinoma is confirmed by the presence of endogenous hyperinsulinemic hypoglycaemia. A diagnostic "gold standard" for insulinoma is the 72-hour fast test<sup>6</sup>. One third of patients develops corresponding symptoms within 12 hours, 80% within 24 hours, 90% within 48 hours and almost 100% of patients within 72 hours after test initiation<sup>7</sup>. Because of the size of insulinomas (< 2 cm in diameter usually), it is usually difficult to determine their localization. In a number of cases it is impossible to determine insulinoma localization before the operation<sup>1,3</sup>. All diagnostic procedures for insulinoma localization could be preoperative and intraoperative. They include: transabdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy, endoscopic ultrasound (EUS), angiography, arterial stimulation with venous sampling (ASVS), fluorine-18-L-dihydroxyphenylalanine (<sup>18</sup>F-DOPA) positron emission tomography and glucagon-like peptide (GLP) 1-receptor scintigraphy, bidigital palpation and intraoperative ultrasound<sup>3,8-11</sup>. The only curative therapy for those with insulinoma is operative treatment. As approximately 90% of insulinomas are benign, enucleation of the tumor is the method of choice whenever it is possible to be performed<sup>12,13</sup>. Conservative, medical treatment may control hypoglycaemia in 50–60% of patients with insulinoma, but

this therapy is reserved only for patients not reluctant for surgery on or for those with unresectable metastatic disease<sup>3,4</sup>.

The aim of this study was to evaluate all the patients with insulinoma treated in the Military Medical Academy (MMA), Belgrade, in a 60-year duration period.

## Methods

This retrospective study included 42 patients with the diagnosis of insulinoma treated in the MMA (Belgrade, Serbia) from 1951 to 2012. In all patients demographic characteristics, including gender and age, clinical characteristics (symptoms and signs of the disease, as well as the duration of symptoms before the diagnosis), types of biochemical methods for diagnosis, and diagnostic procedures for insulinoma localization in regard to the number of diagnosed insulinomas were analyzed. Also, the types of surgical procedures, tumor size and localization, postoperative complications and outcome were assessed.

## Results

The first patient with insulinoma was treated in the MMA in 1951<sup>14</sup>. The diagnosis was established on the basis of the clinical picture, Whipple's triade and the 72-hour fast test. Before 1970 in the MMA the diagnostic procedures for insulinoma localization were not performed. Until then, 15 patients with insulinoma and one with malignant insulinoma were treated in the MMA<sup>15</sup>. Thirteen of those patients were operated successfully. After introducing angiography as diagnostic procedure for insulinoma in the MMA in 1970, 16 patients were assessed and in all of them insulinoma localization was confirmed intraoperatively. In the 80s of the last century in the MMA began the usage of the non-invasive methods for insulinoma diagnosis. Since 1983, US has been applied and a small number of insulinomas were localized using this technique. In the same year CT started to be used for insulinoma diagnosis, while MRI was introduced in 1985. In 1992 ASVS was introduced, and EUS 10 years later.

Out of the 42 patients, 29 were women and 13 men (ratio 1.2:1). At the time of diagnosis their median age was 43 (8–77) years. The median time between the onset of symptoms to diagnosis of insulinoma was 3 years (one day – 25 years). The clinical characteristics of the patients are listed in Table 1.

pancreatic head 12/41 (29.2%), pancreatic neck 4/41 (9.7%), processus uncinatus 4/41 (9.7%), pancreas body 6/41 (14.6%), pancreas tail 14/41 (34.1%), and outside of the pancreas 1/41 (2.4%). The size of insulinomas was < 1.0 cm in 7/41 (17%), 1–1.9 cm in 20/41 (49%), 2–2.9 cm in 11/41 (27%), and > 3 cm in 3/41 (7%) of patients.

**The clinical characteristics of 42 patients with insulinoma**

**Table 1**

Neuroglycopenic symptoms	Number of the patients [n (%)]	Adrenergic symptoms	Number of the patients [n (%)]
Disturbance of consciousness	32 (73)	Palpitations	22 (5)
Abnormal behavior	32 (73)	Sweating	23 (53)
Confusion	27 (61)	Tremor	17 (38)
Convulsions	27 (61)	Hunger	23 (53)
Blurred vision	18 (41)		
Amnesia	10 (23)		
Hallucinations	5 (11)		
Weakness	25 (56)		
Nocturia	3 (6)		

The diagnosis of insulinoma was estimated by proving Whipple's triads with 72-hour fast test in 14 patients, and/or by low blood glucose level and hiperinsulinemia. Determination of insulinoma localization was assessed by angiography in 16 (36%) of the patients, by US in 3 of 16 (18.8%) patients, by abdominal CT in 8 of 18 (44.5%) patients, and by MRI in 2 of 8 (25%) patients. Since the introduction of EUS and ASVS as diagnostic procedures in the MMA, insulinoma has been found in 13 of 13 (100%) patients by ASVS, and in 13 of 14 (93%) patients by EUS. The difference between EUS and ASVS and other diagnostic procedures for determination of insulinoma localization was significant ( $p < 0.001$ ). There were 6 patients with occult insulinomas. Of 42 patients, a total of 38 (90.5%) patients underwent operative procedure (Table 2). In all the operated patients the open surgical procedure was performed.

## Discussion

Insulinomas are rare endocrine tumors developed from pancreatic beta cells with the incidence about 1 in 250,000 patient-years<sup>16</sup>. As in our series, insulinomas are more common in female patients with the median age at the diagnosis of 47 years approximately<sup>17</sup>. About 90% of insulinomas are single, benign and sporadic tumors that are located in the pancreas, but about 10% of patients with insulinomas have MEN-1. Those patients are often presented with multiple insulinomas and other secreting or non-secreting endocrine tumors. Finally, a particular condition is malignant insulinoma, also found in about 10% of insulinoma patients<sup>18</sup>. Insulinomas are the most common pancreatic endocrine neoplasms present with a typical clinical syndrome known as Whipple's triad. Patients will often present with a profound syncopal episode and will admit to similar less severe episodes in the recent past. They also may admit to palpitations, trembling, diaphoresis, confusion, seizure, and family members may report that the patient has undergone a personality change<sup>5</sup>. The most common clinical symptoms and signs in our patients were disturbance of consciousness and abnormal behavior in 73% of patients, confusion and convulsions in 61% of patients. A wide spectrum of clinical manifestations in patients with insulinoma as well as a large number of diseases that have similar symptoms and signs, may be the reasons for difficult recognition of disease and explain a long period between the onset of symptoms and the diagnosis. In the literature, the time from the onset of symptoms to insulinoma diagnosis varies widely, from 10 days to more than 20 years<sup>19,20</sup>, as in our patients. Since surgery is the only curative treatment of insulinomas, topographic assessment of insulinoma must be performed after the conformation of biological diagnosis of hypoglycemia related to inappropriate insulin secretion. Although intraoperative bidigital palpation and US of the pancreas have been presented as the best methods for detecting insulinomas<sup>18</sup>, radiological examina-

**Table 2**

### Operative procedures on 38 patients with insulinoma

Surgical procedure	n (%)
Tumor enucleation	27 (71)
Distal splenopancreatectomy	8 (21)
Pancreaticoduodenectomy	1 (2.6)
Central pancreatectomy	1 (2.6)
Only laparotomy	1 (2.6)

In 4 of the patients „blind“ distal pancreatectomy was performed due to the cases of occult insulinoma. The second operation was required in 4 (10.5%) patients because of histopathological finding of resected specimens without insulinoma in 3 patients, and early postoperative recurrent hyperinsulinemic hypoglycaemia (unrecognised multicentric insulinoma) in one patient. The overall mortality rate in the postoperative period was 2.6% (one patient). One insulinoma was found in 35 (92%) and two in 3 (8%) of the patients ( $p < 0.001$ ). The distribution of insulinomas was in the

tion must be performed before surgery in order to avoid failure of surgery and reoperations. Insulinomas are usually localized with CT scan and EUS. With the meticulous technique, the sensitivity of multi-slice CT for insulinomas detection could reach 94%<sup>21</sup>. MRI is complementary to CT, in order to confirm the suspected lesion on CT or to search for an insulinoma that CT has not been able to localize. Combining both methods (CT and MRI) the accuracy of insulinomas detection improves. According to our practice CT scan showed to be better than MRI for insulinomas localization, with sensitivity of 44.5% versus 25% on MRI. Technical advances in EUS have led to preoperative identification of > 90% of insulinomas<sup>22</sup>. Even though ASVS is rarely required to localize insulinomas, this method is a valuable tool when conventional imaging is negative. In contrast to the others where the sensitivity of ASVS rarely reached 70%<sup>19, 23</sup>, we had very good results using ASVS for insulinomas localization. Insulinomas were found in all patients who were assessed with ASVS, and in 93% of the patients who were assessed with EUS. We consider that combining EUS and ASVS the sensitivity of insulinomas detection could reach 100%, although those invasive methods were described as a last-line investigation in patients with hypoglycaemia related to endogenous hyperinsulinism.

Improvement in the preoperative diagnostic procedures for insulinomas localization determination enables the surgeon to have an accurate topographic assessment before surgery and to decide about surgical approach preoperatively. However, intraoperative bidigital palpation and US remain the valuable diagnostic methods, as well to confirm previously determined insulinoma localization. There are two types of surgery which can be performed. They include minimal resection (tumor enucleation or central pancreatectomy) and more extended resection (left-sided pancreatectomy with or without spleen-preserving or pancreaticoduodenectomy)<sup>24</sup>. The type of surgery depends on the size and the location of insulinoma and on its relationship with pancreatic duct, vessels and adjacent organs. Tumors located close to the main pancreatic duct and large (> 2 cm) tumors may require a distal pancreatectomy or pancreaticoduodenectomy. In all other cases and whenever it is possible, simple tumor enucleation is the surgical method of choice<sup>12, 13, 25</sup>. We

performed minimal resections in 73.6% of the patients (tumor enucleation in 71% and central pancreatectomy in 2.6% of the patients). Although there were 14 (34%) patients with insulinoma > 2 cm in diameter, the major resections were performed only in 9 (23.6%) of the operated patients (distal splenopancreatectomy in 8 and pancreaticoduodenectomy in one patient). When insulinoma is localized preoperatively with accuracy, enucleation or left-sided pancreatectomy by laparoscopy is performed in many expert medical institutions. It reduces hospital stay duration and improves postoperative quality of life<sup>13, 24, 26</sup>. A "blind" distal pancreatectomy was proposed several years ago in cases with insulinoma not found intra-operatively. However, in such cases where no insulinoma was found intraoperatively, it is recommended today to finish the operation and plan the additional procedures in order to localize insulinoma, including invasive techniques<sup>27</sup>. Before the introduction of EUS and ASVS in the MMA, a "blind" distal pancreatectomy was performed in one patient. Morbidity and mortality depend on the type of surgery. Mortality is almost 0% for enucleation, but may reach 1–2% for left-sided pancreatectomy and up to 4–5% for pancreaticoduodenectomy<sup>18</sup>. In our series, the mortality rate in a postoperative period was 2.6% (one patient) due to postoperative complications. After enucleation our patients had no complications and reoperations were not needed, so this type of surgical procedure should be performed whenever it is technically possible.

### Conclusion

A spectrum of clinical manifestations in patients with insulinoma could be the reason for difficult recognition of the disease with a long period of time between the onset of symptoms and diagnosis. Although invasive, EUS and ASVS are the best methods for insulinoma localization assessment. Combining these two methods ensures high accuracy in preoperative determination of insulinoma localization. "Blind" distal splenopancreatectomy should be avoided due to the possibility of failure in curing the disease and postoperative complications, while minimal resection such as enucleation should be performed whenever it is possible.

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Received on April 15, 2013.

Revised on July 2, 2013.

Accepted on July 8, 2013.

OnLine-First October, 2013.