

Diagnosis and Insulinoma Management Approach

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Abstract: *The most common pancreatic - producing neuroendocrine tumor is insulinoma, with an incidence estimation 0.4% in the population and recorder for 70% to 75% caused hyperinsulinemia. Some of these findings like palpitations, tremors, diaphoresis are frequently seen as autonomic symptoms, in the other hand, the visual disturbances, seizure, coma, even more the personality changes often seen in neuroglycopenic symptoms. According to standard endocrine test specially 72 hours fasting test can established the suspected case's diagnosis. To find resource secretion of pathological insulin can use procedures non invasive imaging, like CT or MRI when the diagnosis of insulinoma has been established. Surgical removal of the tumor is the definitive treatment and laparoscopic surgery for localized lesions is increasingly reported. For unresectable tumor, preoperative preparation or for unsuitable candidates for surgery, medical treatment is the choice. The purpose of this article is to know more about diagnosis and management of insulinoma.*

Keywords: Insulinoma, Multiple Endocrine Neoplasia, hypoglycemia, Neuroendocrine Pancreatic Tumor

1. Introduction

The most common pancreatic-producing neuroendocrine tumor is insulinoma, with incidence estimation 0.4% in the population and recorder for 70% to 75% caused hyperinsulinemia. Most insulinomas originate sporadically (90%), approximately 5% to 10% of cases are related with hereditary syndromes, like Multiple Endocrine Neoplasia type 1 (MEN1) and less than 10% of lesions are malignant [1,2]. Especially about insulinoma, it needs to be discussed specifically because it is related to the incidence of hypoglycemia. Although curative treatment is a surgical procedure, in the early stages of this disorder either management, diagnostic and treatment often involve internal disease. Conservative therapy is needed before operating action can be carried out [3].

The incidence of insulinoma is 3-4 cases per 1 million population per year, constituting 55% of total neuroendocrine tumors. This type of this tumor can be found in all race. Woman compared to men around 3:2. These tumors rarely occur in children, the average age of the patient is 30-60 years (median 35 years) [3].

2. Definition

Insulinoma (*Islet Cells Adenoma*) is a neuroendocrine tumor originating from the islet cell of the pancreatic Langerhans which produces excess insulin. Most (90%) of these tumors are benign, the rest (10%) are malignant [3].

Due to the effect of the hypoglycemia on neuroglycemic symptoms that usually appear visual difficulties, headache, confusion, disorientation, irrational behavior and coma. And, as a result of excessive catecholamine release secondary to the hypoglycemia many patient have symptoms like sweating, palpitations, and tremor. Usually, these onset are related by fasting [4].

Approximately more than 90% of insulinoma size is small less than 2 cm and 90% commonly single. About 5–15% of insulinoma are malignant, and likely appear only in the

pancreas, evenly distributed in the pancreatic head, body, and tail [4].

All patients with hypoglycemia should be suspected in insulinomas, especially when there is a family history of MEN 1 or history suggesting that attacks are provoked by fasting. Insulin is synthesized as proinsulin, which consists of a 30-amino-acid β chain connected by a 33-amino-acid connecting peptide (C peptide) and a 21-amino-acid α chain. In insulinomas, in addition to increased plasma insulin levels, increased plasma proinsulin levels were also found, and C-peptide levels can be increased [4].

Etiology

Insulinoma is a disease with genetic disorders. The second familial hormone-secreting pancreaticoduodenal neuroendocrine tumor in MEN1 is insulinoma, with 10% prevalence MEN1 in adult. Approximately 10% of all patient with insulinomas is MEN1. Patient with MEN1 and in sporadic cases glucopenic symptoms and fasting hypoglycemia with high insulin, pro insulin or C Peptide have the same clinical features and diagnostic [5].

Pathophysiology

Insulinoma in MEN1 dominant caused by benign tumor of pancreas, although in general, insulin produced by non hypersecreting islet tumor or another tumor colon [5]. Insulin that produced by this tumor secreted incidentally so that in a short term caused blood glucose very fluctuate. Approximately 10% insulinoma is multiple. 50% of multiple insulinoma is *multiple endocrine neoplasia type 1* [3].

Clinical Findings

The major hypoglycemic state is usually caused by endogenous hyperinsulinism. Periodically secretion of insulin which is produced by the tumor often makes a hypoglycemic attack [6]. Some of these findings like palpitations, tremors, diaphoresis are frequently seen as autonomic symptoms, in the other hand, the visual disturbances, seizure, coma, even more the personality changes often seen in neuroglycopenic symptoms [7,8]. The insulinomas may produce inappropriate amount of insulin

which can lead to hypoglycemic state, may be fail to recognize by the physician and resulting a delay in diagnosis^[9]. When the glucose level below 45mg/dl and the plasma level below 50 mg/dl, the neuroglycopenic symptoms are obviously seen. Commonly there are two kind of symptoms of hypoglycaemia that frequently seen, the adrenergic symptoms include tremor, anxiety, palpitation, sweaty, and the neuroglycopenic symptoms include lethargy, dizziness, seizure, amnesia or even more coma.

The well known Whipple’s triad are obviously seen in insulinomas which includes:

- (a) Symptoms of neuroglycopenia
- (b) Low level plasma glucose level (<50mg/dl)
- (c) Relief of symptoms (often within 5–10 min) following glucose administration^[10,11,12].

Definite hyperinsulinism in the presence of hypoglycaemia warrants further investigations to confirm insulinoma.

Table 1: Symptoms and frequency of insulinoma

Neuroglycopenic symptoms	Adrenergic symptoms
Confusion (80%)	Diaphoresis (69%)
Visual disturbances (59%)	Tremors (24%)
Amnesia or coma (47%)	Palpitations (12%)
Abnormal behavior (36%)	Hyperphagia/weight gain (50%)
Seizures (17%)	

Note : Data are from multiple studies^[13,14,15,16].

3. Diagnosis of Insulinoma

In a healthy individuals, the normal blood glucose level inside the body is maintained by the negative feedback mechanism. A reciprocal state happened when the blood glucose level are decreased, it will reduce the production of insulin. However, in a B-cell adenomas, this state won’t happen the production of insulin are not depend by the blood glucose level^[11]. The elevated serum insulin level when the hypoglycaemia state occurs may be the main criteria of insulinomas. The gold standar of insulinoma’s diagnosis is the 72 hours of fasting test, to reveal the whipple’s triad of symptoms. this test requires a hospitalization to supervise the patient. When the test conduct, the patient are in fasting period and allowed to take no-calorie fluids and the exercise are encouraged. Then the blood glucose measured until reach 60mg/dl in first 6 hours, and measured hourly until reach 40-50 mg/dl. When the hypoglycaemia symptoms revealed, the blood sample should be taken for a laboratory test of glucose, sulfonylurea, C-peptide insulin and β-hydroxybutyrate^[43]. Some authors revealed that in first 24h, around 70-80% patients developed a hypoglycaemia, and in 48h around 98% patients developed a hypoglycaemia.^[4]

Table 2: Diagnosis of insulinoma^[17,18,19]

Classic diagnostic criteria :
<ul style="list-style-type: none"> • Hypoglycemic state (Blood sugar less than 50 mg/dl) • Neuroglycopenic - phenomenon • Rapid relief of symptoms after glucose administration
Current research
Hypoglycemic state within 72hours fasting test:
<ul style="list-style-type: none"> • The insulin threshold of 5 mIU/L (36 pmol/L) • The C-peptide threshold 0.6 ng/mL (0.2 nmol/L)

- Insulin/C-peptide ratio < 1.0
- 20 pmol/L proinsulin cut-off level
- Sulfonylurea-free or Metabolites-free inside the plasma or urine.

Criteria Diagnosis of Insulinoma^[15] :

- 1) Blood glucose lower than 50 mg/dL with hypoglycaemic symptoms
- 2) Symptoms disappear after meal
- 3) Elevating C-peptide (>200 pmol/L)
- 4) There is no plasma sulfonylurea
- 5) Increased serum insulin level (>5–10 mU/mL)
- 6) Increased proinsulin level (≥25% or ≥22 pmol).

In addition to the 72 hours fasting test there are several test that can be done for insulinoma diagnosis :

a) Intravenous secretin test

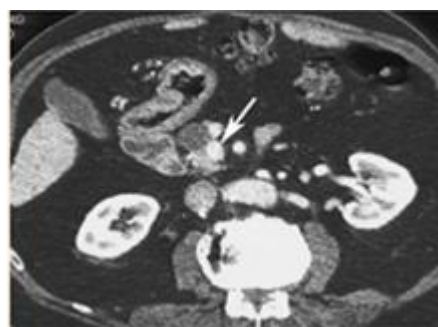
Unlike in the normal population, beta cells of pancreas are insensitive to secretin in patients of insulinoma. An intravenous injection of secretin 2 units/kg causes rise in plasma insulin more than 200% in a normal individual. However, injection of secretin did not stimulate insulin secretion because insulinoma cells are unresponsiveness to secretin in insulinoma.^[11,20]

b) C-Peptide inhibition test with hog insulin

In healthy persons, to decrease in plasma C-peptide levels can use infusion of hog insulin for 1 h leads, were observed in insulinoma patient^[11,21].

c) Non-invasive Imaging

For localizing of a suspected insulinoma, non invasive techniques are available like CT, transabdominal ultrasonography and MRI. Approximately 9%-64% sensitivity of transabdominal ultrasonography in localizing insulinoma^[22]. Sensitivity imaged with both CT and MRI has been reported 33%-64% and 40%-90% because insulinoma demonstrate characteristic features^[23,24]. MRI’s sensitivity and specificity is more preferable than CT to detect the extra pancreatic extension^[25].



Gambar 1. :Insulinoma in 87 years old, male with hypoglycemia. Dual phase CT through pancreatic demonstration. Lesions in 1 cm high looked well (arrow)^[26].

Recent research shows that MRI is more preferable to identify small-scale insulinomas. MRI has a high accuracy around 85% -95 % in detecting insulinoma, even more for the metastases. As well as Computerized Tomography, MRI also a noninvasive examination, time saving, secure, and simplify locate metastases. Commonly insulinomas revealed poor signal intensity on T1-weighted images however,

insulinoma revealed a great signal intensity on T2-weighted images^[27].

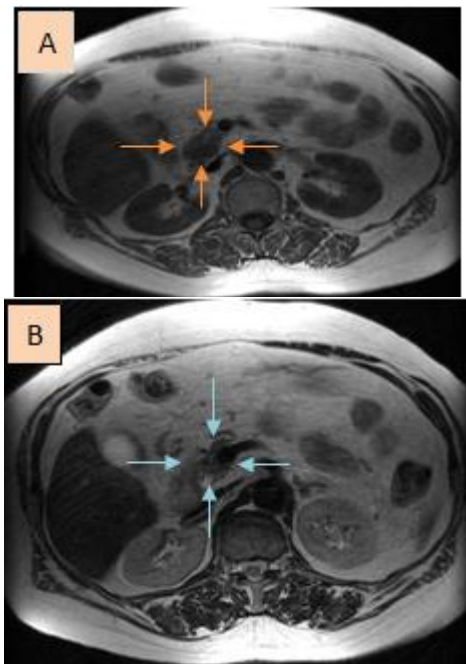


Figure 2: Magnetic resonance imaging of insulinoma of the pancreas

Insulinomas (arrows) generally demonstrate low signal intensity on T1-weighted images (A) and high signal intensity on T2-weighted images (B).

a) Invasive Diagnostic Modalities

Endocrine examinations, mainly 72 hours fasting test is standard diagnostic procedure for suspected insulinoma case. After diagnosis insulinoma established we must know the resource secretion of pathological insulin with non invasive imaging procedure^[28]. Perioperative insulinoma with EUS and ASVS modalities to be proven very accurate to localization of insulinoma and have more preferable than non invasive localization techniques. Currently the most choice examination in Western Centers is EUS with a detection rate 86,6%-92,3%^[24,29]. EUS insulinoma looks typical, with most of the tumors being hypoechoic homogeneous, round in shape, and with different margins (Figure 3).

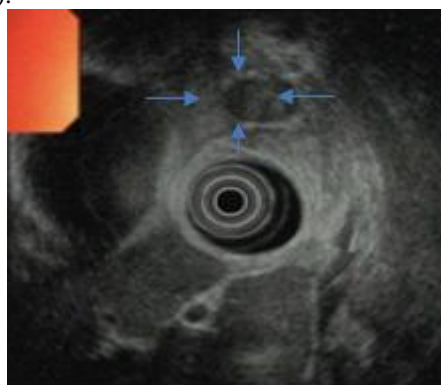


Figure 3: Endoscopic ultrasound features of insulinoma of the pancreas. The appearance of insulinomas (arrows) on endoscopic ultrasonography is quite characteristic, with most tumors homogeneously hypoechoic, rounded in shape, and with distinct margins

There are some problems in tumor detection by EUS, while in the other hand EUS has a high reliability procedure in preoperative insulinoma diagnostic. Firstly, the EUS is an operator dependent so that the result of the EUS may contain false positive or false negative results^[28]. Secondly, when the EUS performed, they often showed a full isoechoic appearance that can make the preoperative insulinoma's diagnostic being missed. Some of the risk factors for false negative such as poor BMI, juvenile and female^[30]. Third, the EUS examination sensitivity is very highly depend on the dimension and region of the tumor in detecting insulinoma. When using the EUS, the pancreatic head revealed the greatest sensitivity while on the other hand the pancreatic tail or extra pancreatic revealed the lowest sensitivity shown by EUS^[24]. Preoperative diagnostic of insulinoma in pancreas can use Fine Needle Aspiration (FNA). The latest invention in EUS has made the EUS guided FNA is very helpful in insulinoma's diagnostic, because most tumors are small^[31]. There is still a controversy that a combination between angiography and ASVS shall not overtaking the non invasive diagnostic such as Computerized Tomography and MRI, yet it still have a superior sensitivity for localizing the right and easy insulinoma which will provide more information for EUS^[32]. ASVS helps regionalize tumors by agreeing with the function of hormones.

Surgical ASVS is more precise and can be supported for reoperation^[24]. The sensibility of ASVS in detecting insulinomas counted between 94% and 100%^[33,34]. Using ASVS, insulinoma was chosen as a clear round or oval blusher that improved vascularization compared to parenchyma throughout the normal pancreas (Figure 4)

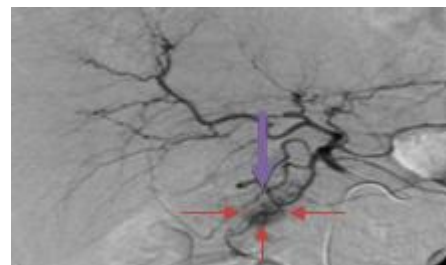


Figure 4: Angiography and arterial stimulation venous sampling. Using arterial stimulation venous sampling, insulinomas (arrows) are seen as well-defined, round or oval vascular blushes that are of increased vascularity compared with the surrounding normal pancreatic parenchyma.

The presence of insulinoma by ASVS are influenced by hyperosmolar concentration in the blood vessels which may lead to cell degradation in the neoplasm, releasing insulin inside the portal vein, so that the insulin are detected in the venous blood sample which came from hepatic vein^[32].

4. Management of Insulinoma

a) Medical Management

Often light insulinoma is successfully overcome by eating (diet) and this is a pillar of conservative treatment. Proper meal scheduling can overcome or prevent hypoglycemia. In principle, shortening the distance between two mealtimes. If necessary to have a dinner schedule before sleep (at 11

pm). Likewise, a variety of eating schedules can be done at midday and at night. Keep in mind to avoid carbohydrates that are quickly absorbed (glucose), carbohydrates that are absorbed relatively longer (flour, bread, potatoes, rice) should be used so as not to stimulate insulin secretion immediately^[3]. Dextrose infusion when more severe situation can be immediately given to treat hypoglycemia. Conservative therapy to treat hypoglycemia in insulinoma is the same as dealing with the incidence of hypoglycemia. Efforts to stabilize blood glucose are also important before surgery. If the effort to treat hypoglycemia is not successful by the methods above, several types of drugs can be used^[3]. Surgery must be performed on a malignant insulinomas after an appropriate imaging^[4]. In different research, 75–100% of patients get well by surgery. Hypoglycemia can controlled by use of diazoxide (150–800 mg/dl) and frequent small meals before surgery. Diazoxide is a benzothiadiazide whose hyperglycemic effect is attributed to inhibition of insulin release. Diazoxide have side effects on GI symptoms such as sodium retention and nausea. Many Patient (50–60%) respond to diazoxide^[4].

Diphenylhydantoin and verapamil also effective to control patient with hypoglycemia. Approximately 40 % patient are effective with long acting somatostatin analogues such as lanreotide and octreotide. Octreotide can inhibits growth hormone secretion and can change plasma glucagon level so that octreotide must be use carefully and also in some patient can worsen the hypoglycemia^[4].

b) Surgical Management

Definitive treatment is surgical excision of the tumors. The surgery of choice in recent days is Laparoscopic resection^[15]. Although the choice treatment of all benign insulinoma is enucleation, intraparenchymal insulinomas may be missed and may require distal or partial pancreatectomy. But, wider resection for small tumors with the advance in diagnostic and localisation techniques is not recommended anymore^[35]. Intraoperative USG and careful surgical palpation has been reported 83% - 98% in identifying small insulinomas [15,36]. Management of insulinomas with laparoscopic more popular, and have been reported few series of successful laparoscopic insulinoma surgery [37, 38, 39, 40, 41, 42, 43]. The preoperative test to locate the tumor is highly needed in a minimal invasive surgery, because the surgical approach depend on the result of the test [37,38]. Furthermore, when there is a small tumor or the tumor can not be palpated, at that time the laparoscopic intraoperative sonography leads to find the anatomical system of the tumor, their relationship with the pancreatic duct and their vascularization [37, 38, 41, 42, 43].

Laparoscopic intraoperative ultrasonography with laparoscopic exploration can highly determine around 86 – 90% of insulinomas, when compared with open exploration using IOUS [38, 40]. Evolving technique is still a laparoscopic surgery for insulinomas, which may shorten the hospitalization stay and precipitate the recovery time [37, 38, 41, 44].

5. Conclusion

The most common pancreatic - producing neuroendocrine tumor is insulinoma with an incidence estimated 0.4% in the population and account for 70 to 75 % of the causes of hyperinsulinemia. Insulinoma have symptoms like dizziness, confusion, and palpitations that improve by consuming carbohydrates. A combination of clinical, biochemical, and imaging tests must be performed to confirm the diagnosis. The treatment of choice is surgical resection of the tumor. To localize the tumor is highly recommended to use intraoperative ultrasound.

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