Insulinoma in Iran: a 20-year review

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BACKGROUND: The time between onset of symptoms of insulinoma to diagnosis ranges from 10 days to more than 20 years. To help physicians make an earlier diagnosis, we defined the clinical, imaging and paraclinical characteristics of insulinoma in cases from seven referral hospitals in Iran over two decades.

METHODS: The medical records of 68 cases with biochemical or histological evidences of insulinoma were reviewed.

RESULTS: More males were affected (53%). The mean age at diagnosis was 39±15.3 years. The mean duration of symptoms was 39.9±59.3 months. Eighty-four percent of patients had been initially misdiagnosed as cereberovascular accident (CVA), epilepsy, conversion disorder, and others). Neuroadrenergic symptoms were observed in 89.6% and and neuroglycopenic symptoms in 97% of patients. Mean diameter of tumours was 2.9 cm (range, 1 cm to 8.5 cm). Of 52 pathologically confirmed cases of insulinoma, 43 tumours (87.8%) were single and 49 (94.2%) were benign. Fifty-five patients had undergone surgery, with a successful outcome in 44 (80%).

CONCLUSION: The high incidence of neuroglycopenic symptoms suggest the clinical impression of insulinoma when patients present with a suggestive clinical syndrome. The clinical impression is essential to decrease the frequent delay in the diagnosis of insulinoma.

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Accepted for publication
August 2005

Ann Saudi Med 2005;25(6):477-480

Insulinomas are functionally characterized by inappropriate release of insulin and/or precursor molecules, usually resulting in a hypoglycemic syndrome. Insulinomas have an estimated incidence of four cases per million person-years.[1] The diagnosis of hyperinsulinemic hypoglycemia is often delayed. Reported intervals between the onset of symptoms to the time of diagnosis range from 10 days to more than 20 years.[2] Although a variety of motor, sensory and mental symptoms have been described with insulinomas, psychiatric and neurologic problems are the most frequent diagnoses before the identification of the tumour.[2,3]

The purpose of this retrospective analysis was to describe clinical (typical symptoms) and biochemical features of patients with insulinomas, which may help physicians to identify patients with an insulinoma earlier, thus shortening the lag between the onset of symptoms and the diagnosis.

Methods

In this retrospective study, the records of all patients (68 cases, 32 female, 36 male) with biochemical or pathologic evidence of insulinoma, who were admitted to seven university hospitals between years 1977-

1996, were identified and reviewed. In addition to a confirmatory pathologic study, a positive 72-hour or overnight fast, defined as either the development of neuroglycopenic or autonomic symptoms with hypoglycemia, or an insulin (mU/mL) to glucose (mg/dL) ratio >0.3, was obligatory for the diagnosis of insulinoma.

The clinical presentation, preoperative localization studies and surgical treatment pathology of resected specimen were abstracted. Time before diagnosis was defined from the onset of suggestive symptoms to the confirmation of the diagnosis. Localization studies identified in the medical records included the CT scan, ultrasonography (transabdominal), and angiography. The numeric results in this article are presented as mean±SD. All data were not available for all cases due to defects in medical records.

Results

A slightly higher proportion of men were affected (53%). The mean age of patients was 39.0±15.3 years (range 10-75 years, males 39.6±15.7 years; females 38.2±15.2 years). Upon admission, the diagnosis of insulinoma was established in only 11 patients. Others had been admitted with diagnoses such as conversion disorder, CVA epilepsy, migraine and depression. In fact, 47 (69.1%) patients had first been referred to neurology and eight patients (11%) to psychiatry services. The mean duration of symptoms by the time that insulinoma was confirmed was 39.9 months.

Mean fasting blood glucose level was 32.5±16.3 mg/dL. Neuroglycopenic signs, the most common clinical findings, were present in 66 patients (97%) (Table 1). We found orthostatic hypotension in only 16.6% of our patients. Three patients had a positive family history of insulinoma. Two patients had a diagnoses of familial multiple endocrine neoplasia type I (MEN I), based on the presence of tumours in at least one more principal organ (parathyroid or anterior pituitary). Hypoglycaemia developed in 53 patients on fasting and in 15 after exercise. The mean frequency of hypoglycaemic episodes was 1±1.4 per day with frequent report of episodes lasting more than an hour. The classic Whipple triad was present in 64 patients (94.1%).

Table 1. Clinical picture of insulinoma in 68 cases.

Signs or symptoms	Number of patients	Percentage
Adrenergic		89.6
Weakness	59	88.1
Palpitation	57	85.1
Perspiration	58	86.6
Neuroglycopenic		97.0
Confusion and behaviour disorder	47	70.0
Coma	49	73.1
Seizure	33	50

The histopathological and biochemical approaches alone were applied for diagnosis in 23 and 16 patients, respectively. Both approaches were used in an additional 29 patients. The biochemical diagnosis of insulinoma was established in 45 patients in whom overnight fasting had led to hypoglycaemia (blood glucose levels below 40 mg/dL) accompanied by high insulin levels (mean insulin=67.3±112.9 μIU/mL; mean insulin/glucose ratio=2.02±2.0). The diagnosis of insulinoma was histologically confirmed in 52 patients (76%). Solitary tumours constituted 87.8% (n=43) of cases (33.3% located in the head, 26.1% in the body and 40.4% in the tail). Mean tumour size was 2.9 cm (range, 1-8.5 cm). Most tumours (n=49) were benign (94.2%). Three patients had malignant tumours. The diagnosis was based on local invasion; no patient had evidence of distant metastasis. Nesidioblastosis was reported in three cases. Macroscopic examination of the resected pancreas and microscopic examination of pancreatic specimens sliced completely in 2-4 mm thick slices showed no focal abnormality in these two cases. Preoperative ultrasonography, CT scan (non-spiral) and angiography (non-selective) success rates are shown in Table 2.

Fifty-five patients underwent surgery. The method in 38 patients was enucleation of the tumour and in 17 partial resection of the pancreas. Sixteen patients experienced post-surgical complications. Within one week after surgery, 44 patients, all of whom survived, had good glycemic control. Insulinoma recurred in only one of these patients 3 years after surgery. Five patients died; one patient died during the operation and four during the first week following (on days 2, 3, 5 and 7 after the operation). Two patients, whose hypoglycemia persisted, remained in need of medical treatment. Therefore, surgery was successful in 39 patients (70%). Thirteen patients did not undergo surgery, in most cases due to advanced age (>65 years) and/or patient refusal.

Discussion

Primary β-cell disorders are the most common

Table 2. Preoperative imaging studies.

	Angiography	CT scan	Ultrasonography
Total	35	60	50
Certain*	9 (25.7%)	15 (30%)	10 (20%)
Doubtful†	1 (2.8%)	5 (10%)	4 (8%)
Negative	24 (68.5%)	37 (74%)	35 (70%)
False	1 (2.8%)	3 (6%)	1 (2%)

*When the radiologist clearly indicated the presence of the lesion
†When the radiologist was suspicious of the lesion

cause of hypoglycemia due to endogenous hyperinsulinism. Insulinoma is a rare disease and should therefore be considered in patients with hypoglycaemia. Compared with previous studies, it seems that insulinoma affects Iranian patients at younger ages (Table 3). The mean age in our study was 39 years, which is lower than that reported in other series (generally above 45 years).[1,2,4-7] An inconsistency in the findings of this study with other studies was also noticeable in the slight predominance of male patients while most reports indicate, particularly in benign cases, that females are affected more frequently.[8,9] In fact, the female/male ratio may reach as high as 2 to 1.[10,11]

In this study, patients had presented most commonly with neuroglycopenic signs and symptoms, which agrees well with previous reports.[7] However, seizure was recorded in nearly half; this far outnumbers that reported by Boukhman et al (32%) or Dizon et al (29%).[6,7] Again, high rates of coma or stupor (73%) were found in our study. The high incidence of serious features could have resulted from the delay in the diagnosis of insulinoma.

The tumours were usually small, with 90% less than 2 cm.[1,2,5,7] The large size of tumours in our study (mean diameter, 2.9 cm) was surprising and may indicate a long delayed diagnosis of insulinoma. Long periods between the onset of symptoms and diagnosis (about 40 months) concur with this claim.

MEN I was found in two patients. In patients with insulinoma, MEN I should be suspected, particularly when the lesion is multiple. Approximately 4% to 10% of patients with hyperinsulinism will have MEN I.[1,12] In a review of 60 cases, 76% of MEN I patients had multiple insulinoma of which 20% were malignant.[13]

Sensitivity of ultrasonography has been reported as 9% to 63%.[9,14] The reported figures for CT scan, MRI and angiography are 16% to 72%,[9,15-17] 11% to 70%,[8,9,18] and 36% to 91%,[9] respectively. Imaging studies were not so successful in preoperative localisation of tumours; these data agree with previous reports.[11,19] Localization of the tumour either before or during surgery can be challenging, in part because of the small size of the tumours and the fact that they can be embedded within the pancreatic head.[20] Actually, a negative imaging study cannot rule out the presence of insulinoma. Blind distal pancre-

Table 3. Comparison with the findings of previous series.

Variables	Current study	Service[1]	Dizon[7]	Boukhman[6]	Fajans[5]	Service[2]
Mean age	39	47	55	46	–	49
Sex predominance	Male	Female	Female	Female	Female	Female
Duration of symptoms (months)	40	33	46	46	–	46
Mean FBS (mg/dl)	32.5	–	–	–	–	37
Proportion of solitary tumors (%)	76.3	81	79	73	76	88
Proportion of Malignant tumors (%)	5.7	9	10	10	6	–
Mean diameter of tumors (cm)	2.9	2	2	1.6	2	2.1
Frequency of MEN I (%)	2.9	7.6	8	16	9	6
Surgery success rate (%)	87.2	–	–	–	–	97.2

atectomy had been the standard surgical therapy when the tumour is not seen or is palpated intraoperatively.[21] However, it seems that with the current preoperative and surgical advances, blind distal pancreatectomy is no longer a logical approach. Modern imaging techniques, however, are able to diagnose small tumours with high sensitivity. Some authors suppose that endoscopic ultrasonography or arteriography with calcium stimulation are the most sensitive ways to detect insulinomas,[8,16,20] while others believe that the hands of the skilled surgeon can find the tumour better than any imaging techniques.[14] Postsurgical recovery was 87.3% in this study, which is comparable to the literature, indicating rates between 75% to 95%.[22] Enucleation can be done when intraoperative findings of the tumour and regional lymph nodes indicate neither malignant features nor multiple lesions. In lesions that do not involve the main pancreatic duct or are not located on the tail, enucleation is favored as well. For the first operation, enucleation is still the procedure of choice, even for the malignant insulinoma in the head with a well-defined capsule and no metastatic lesions, the objective being to avoid a duodenopancreatectomy or total pancreatectomy.[1] Most insulinomas show good prognosis after resection of the primary tumours. However, about 10% of these tumours are malignant, and in such patients relapse and metastases are frequently observed, along with the reappearance of hypoglycemic episodes.[23]

In conclusion, we presented the picture of insulinoma patients in seven hospitals in Iran. High rates of advanced disease, as indicated by the large size of the tumours and the long delay between onset of symptoms and clinical diagnosis of insulinoma, make it urgent that medical professionals should be suspicious about insulinoma when a patient presents with an indicating clinical syndrome. The long delay in treatment of patients can be reduced, leading to better health care and decreasing unnecessary expenses.

Author contributions: B Larijani designed the study; S Aghakhani and F Zahedi wrote the first draft of article; SS Moosavi Lor was chief manager; M Pajouhi and MH Bastanhagh managed and supervised the study.

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