

Two clinical cases of insulinoma misdiagnosed as psychiatric conditions

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Abstract. We describe the clinical cases of two male subjects, respectively 73 and 41 years old, affected with insulinoma, misdiagnosed for many years as psychiatric subjects and scarcely responsive to therapy with benzodiazepins, antidepressants and antiepileptics. Although Whipple's triad was satisfied in both subjects since the onset of symptoms, they had to wait a long time for the correct diagnosis and appropriate treatment. Once the surgical therapy was carried out, our subjects recovered totally and ended the psycho-drugs.

Key words: Insulinoma, epilepsy, neuroglycopenia

Introduction

The Insulinomas are rare tumours of the Langerhans islets of the pancreas and are benign in the majority of cases (>90%). They are the most common type of pancreatic endocrine neoplasm, occurring in 1-5 per million of the population per year. Moreover, these tumours sporadically occur as part of the Multiple Endocrine Neoplasia Syndrome type I (MEN I) (1). Although these types of tumours cause hyperinsulinism and hypoglycaemia, severe asthenia, profuse diaphoresis and tremors, they sometimes present neurologic symptoms, so they are very often undiagnosed or misdiagnosed as behaviour disturbances or psychiatric conditions (2). For this reason, the diagnosis is sometimes delayed and, in fact, it has been calculated that the interval from onset of symptoms and time of diagnosis ranges from 10 days to more than 20 years (3).

The delay of diagnosis is probably due to prevalent neuroglycopenic symptoms conditioning psychiatric and neurologic problems such as confusion, personality changes, bizarre behaviour, weight gain, amnesia, diplopia, dizziness, irritability, seizures, drowsiness, loss of consciousness, and coma (4-8).

The major criteria for diagnosis of insulinoma are an insulin dosage >6 μ U/ml and a dosable serum C-peptide coherent with symptoms of hypoglycaemia and fasting glycaemia <45 mg/dl. Clinically the presence of Whipple's triad, consisting in symptoms related to hypoglycaemia, glycaemia <45-50 mg/dl, and considerable improvement with glucose administration, strongly suggests the suspicion of insulinoma (9).

After clinical suspicion and laboratory confirmation of insulinoma, it is possible to localize exactly the tumour in the pancreas. Although some authors retain that the preoperative localization of insulinomas is not necessary, imaging techniques, such as CT-scan, MR, endoscopic ultrasound and intraoperative ultrasonography can help to localize the tumour (10).

Once the diagnosis of insulinoma is made, the most common form of management is surgical with or without previous octreotide treatment ¹¹ which consists in the excision of the lesion varying from a distal pancreatectomy to enucleation of the tumour or to a pancreatico-duodenectomy (12).

Prognosis in surgically treated insulinomas varies depending on whether the disease is benign, malignant or associated with multiple endocrine neoplasia type I (12). Benign spread insulinoma is almost always

curable, whereas relapse is more common in MEN I syndrome and malignant insulinoma has a much poorer prognosis (12, 13). After the excision of the tumour subjects can develop diabetes.

Clinical cases

Case 1

An obese 73-year-old man was admitted to our Emergency Division because of severe asthenia, chills, important sweating and seizures. His clinical history showed, hypertension in the last 4 years, abdominal aorta aneurism that had been surgically treated 4 years before, nightly seizures, sudden behavioural disturbances treated with antidepressant and benzodiazepines, and severe weight gain of 40 Kg due to bulimic crises in the last two years; he was neither a smoker nor an alcohol drinker.

He appeared pale, tachycardic, suffering with important sweating and subsequent tonic-clonic attacks, BP 150/90 mmHg, signs of ventricular hypertrophy at EKG, BMI 37.

The haemo-gluco-test showed a severe hypoglycaemia (26 mg/dl). The subject was treated with hypertonic glucose solution with an important resolution of symptoms.

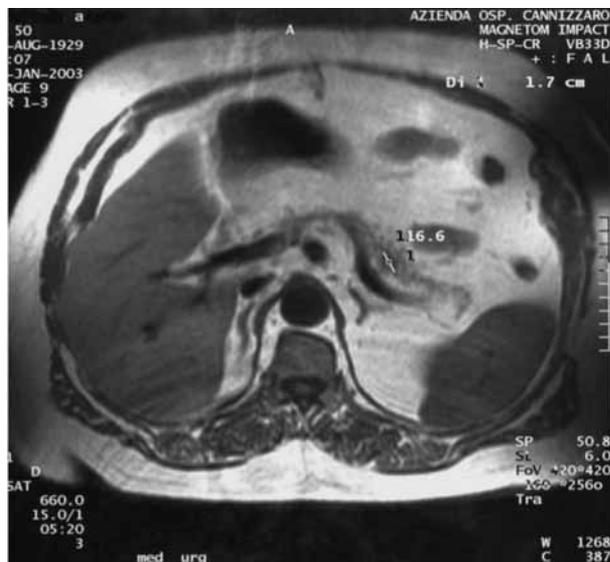


Figure 1. Clinical case n. 1

Laboratory tests pointed out altered insulin (basal insulin 53.72 μ U/ml) and C-peptide (4.9 μ g/ml) dosages, as well as glycaemic levels which resulted low especially in night hours. Ct-scan of the abdomen showed the presence of a nodular image in pancreatic body-tail that was suspicious for insulinoma with no lymph node implication and without other secondaries; MR confirmed this finding (Figs. 1-3). The presence of MEN syndrome was excluded. The subject was submitted to surgical excision of insulinoma. Histological



Figure 2. Clinical case n. 1



Figure 3. Clinical case n. 1

evaluation revealed it to be an adeno-carcinoma with low grade of malignancy (Figs. 4-6).

Three months later the subject became diabetic and started insulin therapy.

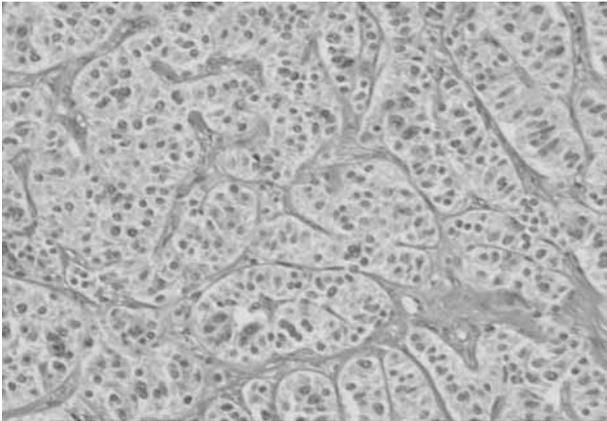


Figure 4. Clinical case n. 1

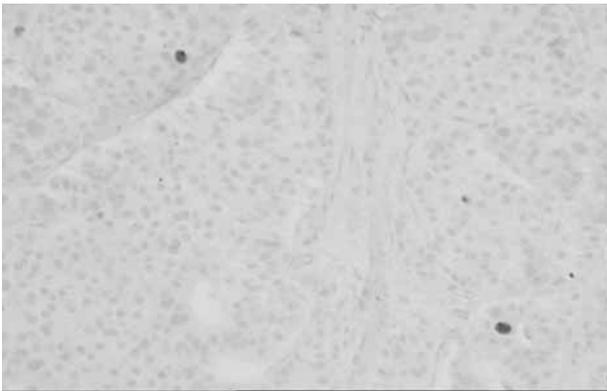


Figure 5. Clinical case n. 1

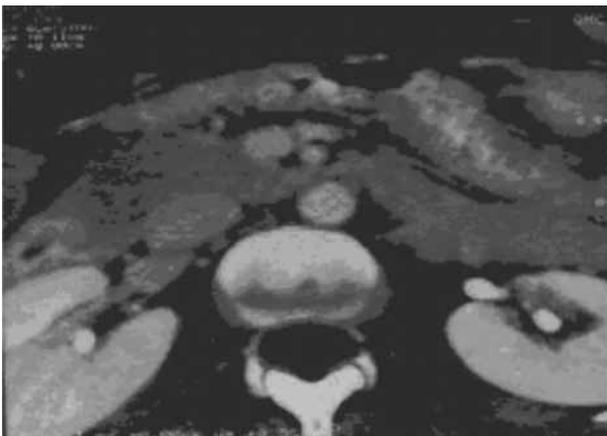


Figure 6. Clinical case n. 2

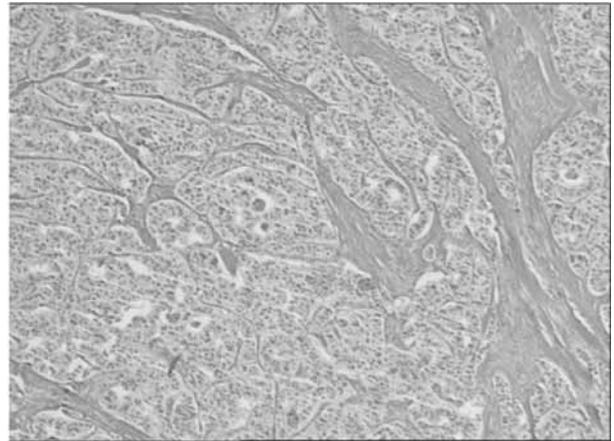


Figure 7. Clinical case n. 2

Case 2

A 41-year-old male subject was admitted to our Division for relapsing nightly hypoglycaemic crises presenting classic Whipple's triad during the last months. At clinical history the diagnosis of epilepsy one year before, that was treated unsuccessfully with Phenobarbital, was pointed out; he was a non-smoker and non-alcohol drinker. He appeared in a good clinical condition, BP 130/80 mmHg, eusphygmic, normal EKG, BMI 27. Submitted to a fasting test, he interrupted it for severe symptomatic hypoglycaemia (30 mg/dl). Laboratory test showed a rise of insulin level (55.82 μ U/ml) and dosable C-peptide (5.82 μ g/dl) that were repeatedly evaluated. CT-scan of the abdomen pointed out a nodular image in the pancreatic hook a process with no lymph node implication; MR confirmed the suspicion of insulinoma (Fig. 6). Total-body-scintiscan revealed no abnormalities. The subject started therapy with octreotide obtaining a good glycaemic control of glycaemia and was then submitted to surgical treatment of insulinoma. Histology showed the absence of an adenoma (Fig. 7).

Discussion

Insulinomas may occur in either sex at any age. They are twice as common in women than in men and 50% of the subjects are over fifty. The majority of insulinomas are sporadic, usually small and benign

(>90%) and occur throughout the pancreas; rarely they are ectopic (1).

In the 1940s, Whipple reported that a wrong diagnosis was responsible for 38% of the unsuccessful surgical explorations for presumed insulinomas. To better detect subjects with insulinomas, Whipple devised his famous axiom: biochemical hypoglycaemia with symptoms that are relieved by the elevation of glucose levels to normal range (9).

However the diagnosis of insulinoma is often delayed as there may be a myriad of symptoms associated with neuroglycopenia, including confusion, neuropathies, blurred vision and an adrenergic response which apparently, due to the rarity of the insulinoma, seem to be strictly related to the tumour itself (4).

An international investigation of 1067 cases showed that neuropsychiatric symptoms including loss of consciousness, sluggishness, confusion, asthenia, deep coma, dizziness, disturbance in vision and epilepsy are present in 92% of the subjects (14). Confusion and personality changes or bizarre behaviour are common symptoms. In fact many subjects are given other diagnosis, especially neurologic disorders (64%), including seizure disorders, and psychiatric disorders (8%). Several subjects are on antiseizure medication at the time of surgery (Dizon).

Although the mean duration of symptoms at the time of presentation has been estimated around 19 months and seems to have decreased in the last few years, delays of more than two years are reported by Goeghegan, who considered cases up to 168 months, and Doherty who described a mean delay of 24 months. Dizon referred that only 28% of the subjects are diagnosed with an insulinoma within one year of the onset of symptoms 53% of the subjects are diagnosed within 5 years, and 19% beyond 5 years (4).

Some subjects (40%) show amnesia of hypoglycaemic events and it is really important to investigate the symptoms with the family. In our first subject the clinical presentation that was suggestive of a neuropsychiatric disorder caused a 4 year diagnostic delay, and in the second case a 2 year delay. Both subjects had been treated for years as psychiatric subjects: the first one as anxious, the second one as epileptic. Moreover, a more accurate and correct investigation showed that earlier diagnosis should have been possi-

ble, since the Whipple's triad was satisfied in both of them. In fact most of our subjects' symptoms were of neuroglycopenic origin and were relieved by the ingestion of food.

Many subjects report an association between symptoms and meals or activity and stress; others report the symptoms during night time. In malignant tumours the postprandial episodes are frequent (1, 2).

In our first subject there was a weight gain of 40 kg; this symptom is aspecific and is reported in only 20% of the subjects (1, 2). However, this symptom must not be under-estimated especially if it is due to "therapeutic" ingestion of foods.

Biochemical tests are the mainstay of diagnosis: the demonstration of high insulin levels in the case of hypoglycaemia; C-peptide assay to exclude factitious hypoglycaemia, as low or absent C-peptide levels suggest exogenous insulin administration; the anti-insulin antibodies frequently present in those subjects are the most frequently used test. However if the diagnosis is not clear and diagnostic results are not obtained after an overnight fast the test of choice is the 72-hours supervised fast. The subject should be active and only water or non caloric infusion should be given. Blood glucose and insulin tests are performed every six hours and are considered positive if insulin is more than 25 pmol/L, C-peptide is more than 75 pmol/L, and glucose level are less than 2.2 mmol/L.

If hypoglycaemia has not occurred after a 72 h fast, 20 minutes of moderate exercises are performed and a final sample of glucose and insulin is taken. If the test is negative, an alternative diagnosis should be considered.

Once the diagnosis of insulinoma has been biochemically confirmed, the issue of whether localizing techniques are of benefit arises. In fact, the assumption that preoperative localization of insulinoma is of benefit at all is still unproven (10). Other authors believe it necessary to give the surgeon information about the tumour and the strategies to plan the operation. Since simple intraoperative palpation of the pancreas detects 75-95% of insulinomas and the more experienced surgeons report only 0,5 % tumours missed on palpation, we believe that preoperative localization is useful but not indispensable (15).

Once the diagnosis of insulinoma has been rea-

ched and the tumour eventually localized, the most common form of treatment is surgical which is either curative or useful in obtaining a good biochemical palliation. In fact, the rare malignant form of the tumour is much more indolent than the more aggressive exocrine pancreatic adenocarcinoma and is curable in a large number of cases while a significant palliation is achievable in those cases that are incurable (16).

Subjects with insulinoma frequently see their physicians with vague and often misleading symptoms. Contacting family members about associated amnesia or changing eating attitude is often very helpful.

The diagnosis of neuroglycopenia should be considered in all the subjects who present common problems such as spells, psychological complaints, altered memory or seizure disorders. Hyperinsulinemic hypoglycaemia is an incapacitating and potentially debilitating condition that is surgically curable. Early recognition may prevent serious adverse consequences including neurological damage.

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