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PANCREATIC INSULINOMA PRESENTING WITH POSTPRANDIAL HYPOGLICEMIAS

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Abstract

We report the case of an obese 58 years old patient evaluated for hypoglycemia. The response to a prolonged fasting test was normal, but symptomatic hypoglycemia ensued after mixed meals and with oral glucose loading. A magnetic resonance scan of the abdomen revealed a pancreatic tail tumor, histologically diagnosed as benign insulinoma after successful laparotomy. „Glucose-responsive" insulinomas, although rare, have been previously described in the literature. Therefore, the diagnosis of insulinoma should also be considered in patients that exhibit postprandial rather than fasting hypoglycemia.

key words: *insulinoma, hyperinsulinemic hypoglycemia, postprandial hypoglycemia.*

Case presentation

A 58 years-old male patient was admitted to „N. C. Paulescu" Institute in March 2009 for medical evaluation of hypoglicemic episodes. Two weeks prior to admission the patient experienced an episode of lipothymia-like symptoms (lightheadedness, palpitations, sweating) followed by transient loss of conscience. The symptoms appeared during postprandial state (2-3 hours after a meal), when the patient was supine, wich implies a moderate physical activity. The ambulance team found the patient partially recovered, conscious, complaining of dizziness, and tested the glycemia upon arrival, with a glucometer, revealing a value of 47 mg/dl. With intravenous glucose administration the patient's state improved slowly over the next hour. Further history taking from the patient revealed similar rare episodes troughout the last year consisting of dizziness, sweating, and lipothymia (without loss of consciousness) which did not prompt the patient to seek medical attention.

Clinical examination after admision was near-normal. It revealed: patient in no apparent distress, height 168 cm, weight 102 kg, BMI 36 kg/mp, abdominal circumference 115 cm, normal respiratory system, normal cardiovasculary system, BP=120/80 mmHg, HR=72 bpm, no palpable masses in the

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abdomen, normal neurological examination. The patient doesn't smoke and rarely drinks alcohol.

Laboratory workup: basal glycemia 67mg/dl, lipid panel: total-cholesterol 186mg/dl, LDL-cholesterol 111mg/dl, HDL-cholesterol 45.6mg/dl, triglycerides 146mg/dl, normal hemogram (WBC=7200/mm3, Hb=16.4g/dl, HCT=51%, PLT=194000/mm3), normal renal function (serum creatinine 0.92mg/dl), no hepatocytolysis, glycated hemoglobin A1c 4.8%.

Resting ECG showed sinus rhythm with right bundle branch block (which the patient did not know of), and no other pathologic changes.

After admission the patient underwent a 72 hours-fast to test for fasting hypoglycemia. Our method consists of every 4 hours sampling for glycemia and insulinemia. The insulinemia is only determined in serum samples with a glycemia under 45 mg/dl, associated with symptoms, to assure a good positive predictive value for hyperinsulinemic hypoglycemia. If the patient experiences symtoms suggestive of hypoglicemia (especially neuroglycopenic symptoms) additional blood samples are obtained. In this case the patient remained totally asymptomatic troughout the 72-hours fast, with glycemias between 82 and 52mg/dl (no insulinemias were determined). We excluded the suspicion of fasting hypoglycemia. We also did an oral glucose tolerance test (OGTT) with 75g of glucose (with samplings at 0, 1, 2 and 3 hours) to asses for the presence of postprandial hypoglycemia. The glicemic values were: 0: 78mg/dl, 1 h: 160mg/dl, 2h: 208mg/dl, 3h: 130mg/dl. Curiously, the 2 hour value was abnormaly high, but given the discordance between the OGTT and the normal HbA1c value (4,8%) we decided to repeat the OGTT at a later date.

The differential dignoses that we discussed are vasovagal sincope (which we considered at the time to be the most probable), cardiac arrhythmias (unconfirmed during admission, still Holter ECG would be indicated), intracranial pathology (improbable given the normal neurological exam), or massive pulmonary thromboembolism (syncope and an unknown RBBB; excluded given the patient's subsequent evolution).

The patient was discharged with the diagnosis of grade I obesity and right bundle brach block, referred to internal medicine for further workup of the syncopal episode, and recalled in our clinic in 2 weeks to repeat the OGTT.

He returned after 1 month in which he was asymptomatic and did not undergo any further medical workup. We repeated the OGTT with sampling of glycemia and insulinemia at 0, 1, 2, 3, and 4 hours. The patient was completely asymptomatic throughout the test, but he was found with low glycemic values at 2 and 3 hours, with increased insulinemia: 2h: glycemia 28mg/dl, insulinemia 51.89µUI/ml; 3h: glycemia 38mg/dl, insulinemia 16.74µUI/ml. We also tested the patient after mixed meals, revealing low glycemic values (<55mg/dl), with inadequately high insulinemic and C-peptide values (e.g glycemia 50mg/dl, insulinemia 8.87µUI/ml, C-peptide 4,37ng/ml), some of them accompanied by symptoms suggestive of neuroglycopenia (dizziness, visual disturbances). Imagistic evaluation of the abdomen was done employing echography and contrast-enhanced computerised tomography. Abdominal ultrasound revealed liver steatosis. Abdominal CT confirmed the

liver steatosis, and also found a small serous cyst in liver segment III. The pancreas had normal dimensions and was homogenous. On both kydneys we found multiple small cortical cysts. No tumors were found anywhere in the abdomen or retroperitoneum. Postprandial hiperinsulinemic hypoglycemia of unknown etiology was diagnosed.

The pacient was started on a low-glycemic index, high-fiber, no-alcohol diet, with multiple meals and snacks daily to avoid episodes of hypoglycemia. He was given a glucometer and instructed to monitor his glycemic levels 2-3 hours after meals, and when symptoms develop. He was also instructed not to drive and to avoid working at heights.

He was again reevaluated after 2 weeks, during which he recorded several episodes of postprandial hypoglycemia, almost all of them asymptomatic. We started diazoxide (an insulin release inhibitor) 100mg tid, which resulted in a modest increase of basal glycemia, but had almost no effect on postprandial glycemic values. The patient was refferred for endoscopic echographic evaluation of the pancreas. The examination revealed two hypoecogenic formations of 3,3 and 3,7mm, in the body and head of the pancreas, respectively, tumoral or vascular in nature (their characterisation could not be done because of lack of Doppler imaging).

We decided to postpone exploratory laparotomy, and to start the patient on acarbose (intestinal glucosidase inhibitor) 50mg tid, up-titrated after one week to 100 mg tid. The therapy proved partially successful together with the dietary approach. Postprandial glycemic values recorded on the patient glucometer increased (52-93mg/dl at 2 hours after meals), with only few hypoglycemic episodes (after high-glycemic index meals).

In June 2010 the patient was admitted with severe hypoglycemia at another hospital and then transfered to the „N. C. Paulescu" Institute. He was found by his family unconscious, with a glycemic value of 28mg/dl, at 2 hours after a meal that contained rapidly absorbed carbohydrates. We scheduled him for a magnetic resonance scan of the abdomen that was done in July 2010, and revealed a 28/32/21mm tumor on the antero-inferior aspect of the pancreatic tail. In the same month he was admitted in the Surgical Clinic of „I. Cantacuzino" Hospital and underwent laparotomy. Intrasurgical palpation of the pancreas revealed a well delimited 2,5cm tumor on the anterior aspect of the tail. Enucleation of the tumor was performed.

On pathological examination the tumor consisted of round cells with eosinophilic cytoplasm, with a tubulo-trabecular and gyriform disposition pattern and extensive areas of hyalinization of the stromal tissue. Minimal nuclear atypias were present. Immunohistochemical examination confirmed the presence of diffuse insulin staining, chromogranin in some of the cells, and absence of glucagon staining. Vimentin staining was positive in the stromal tissue and negative in tumoral cells. Also, the proliferation marker Ki67 was positive in only about 1% of tumor cells. Pathology confirmed a well differentiated benign insulinoma of the pancreas.

Imediately after surgery the patient's glycemia was monitored hourly, the values recorded being: 67, 53, 56, 37, 69, 185, 110, 170, 165, 291, 163mg/dl. Postoperatory evolution was rapidly favourable. After discharge from the hospital self-monitored

glycemic values were normal. We also recalled the patient to repeat an OGTT at one month after surgery. The glycemic values (0: 96mg/dl, 1 h: 174mg/dl, 2 h: 83mg/dl, 3 h: 76mg/dl) were normal. Subsequent evolution of the case was favourable, with no recurrent symptoms and a normal basal glycemia at about one year, and later at two years after surgery.

Disscusion

Insulinomas are rare endocrine tumors (4 cases per million person-years), but the most common cause of endogenous hyperinsulinemic hypoglycemia [1]. The diagnosis of insulinoma rests on concomitant documentation of hypoglycemia and inadequately high insulin levels in repeated samples of venous plasma. Service recommended a set of biochemical criteria for positive diagnosis in the absence of renal insufficiency: an insulin level of 36pmol/l or more (as measured by radioimmunoassay) or of 18pmol/l or more (as measured by an immunochemiluminiscence assay), a C-peptide level of 200pmol/l or more, and a proinsulin level of 5pmol/l or more in a patient with a serum glucose level of 45mg/dl or less, with negative plasma screens for sulphonylurea and insulin antibodies [2]. The classic 72-hours (or 48-hours as more recently was suggested [3]) supervised fasting test is employed in order to precipitate hypoglycemia. The fasting has two objectives: firstly, to confirm that the patients' symptoms are indeed caused by hypoglycemia, and secondly, to confirm the presence of concomitant hyperinsulinemia. In theory, 75% of insulinomas are diagnosed during 24 hours of fasting and about 90-95% in 48 hours, whereas the absence of hypoglycemia for 72 hours is generally considered to exclude the diagnosis of insulinoma. The second important step in the workup of insulinoma patients is the localisation of the culprit tumor, a task which can be very difficult sometimes. Abdominal computerised tomodensitometry or magnetic resonance and endoscopic echography are the main imaging methods that give good results. In some cases exploratory laparothomy with direct palpation of the pancreas, intraoperatory echography, and/or calcium injections in the arteries supplying the pancreas must be used for successful localisation of the insulinoma [4].

Exclusive postprandial hypoglycemia in the presence of β-cell pathology is considered the hallmark of islet β-cell hyperplasia (nesidioblastosis), described mostly in children. A few cases exhibiting such characteristics have also been reported following weight-loss surgery [5, 6].

In this report, we present the case of a patient with insulinoma and the absence of hypoglycemia even after 72 or more hours of fasting, during several attempts, but with repeteated documentation of postprandial hyperinsulinemic hypoglycemia. To date, several case reports on insulinoma patients who exhibited postprandial hypoglycemia have been published [7, 8, 9]. Recently, Placzkowski et al reported that 6% (13 of 214) of the patients at the Mayo Clinic certain presented with postprandial hypoglycemia, 3 of the cases with negative supervised fasts, suggesting that insulinomas have diverse characteristics [10]. A glucagon injection test is sometimes used in order to precipitate hypoglycemia in patients with normal glycemic values even after prolonged fasting [8, 9]. In our patient hyperinsulinemic hypoglycemia was precipitated by mixed

meals and also appeared after oral glucose load. Following one rapidly absorbed carbohydrates meal the patient even suffered a severe hypoglycemia, with comatous state, which is also rare with postprandial hypoglycemias.

This case underlines the importance of considering the diagnosis of insulinoma also in patients with postprandial, rather than fasting hypoglycemia. As in our case, the right diagnosis requires adherence to a reliable, comprehensive method and sometimes patient observation over an extended period of time.

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