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Insulinoma

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Summary Spontaneous hypoglycemia is rare. However, in healthy individuals with recurrent symptoms of spontaneous hypoglycemia, an insulinoma should be suspected. Patients with an insulinoma typically present with neuroglycopenic symptoms and are commonly misdiagnosed as having a psychiatric or neurologic disorder. The hallmark of these tumors is random hypoglycemia (not reactive) with inappropriately elevated endogenous insulin levels. We report the case of a 44-year-old female with an insulinoma. We will then review the current recommendations for the diagnosis and management of these rare tumors.

A 44-year-old white female was found by her husband at home confused, shaking, and diaphoretic. The husband was alerted by one of her coworkers that she did not show up that morning for work. He took her immediately to her family physician's office for evaluation, where her fingerstick glucose showed a reading of 24 mg/dL. She was given an oral glucose solution with subsequent return of her glucose level to 87 mg/dL and resolution of her symptoms. The patient stated that she had been experiencing similar episodes two to three times per month for the past 4 months. Her symptoms included disorientation, confusion, shaking, sweating, tunnel vision, and amnesia of the episode. Episodes typically occurred in the morning, lasted anywhere from 1 to 6 hours, and occurred without regard to meals. The symptoms were more frequent and severe during her menstrual cycle and they occurred more often when she was more physically active. Her symptoms were relieved with food.

She had no known medical problems or previous surgeries. Her only medication was a multivitamin daily and she did not take any supplements or prescription medications. Her family history was non-contributory, including no history of diabetes or other endocrine disorders. She did not smoke or use illicit drugs, usually consumed 1 to 2 glasses of wine per week, ate a relatively healthy diet, and exercised regularly. Review of systems was significant for lightheadedness with exertion, with recent symptoms of unexplained weight gain (15 lbs) within the prior 3 months. Physical examination was essentially normal and did not reveal any orthostasis.

The patient was referred to an endocrinologist for evaluation, given a glucometer to monitor her fingerstick glucose level sugars, and instructed to eat 6 regularly scheduled meals rich in carbohydrates during the day. She was also given glucose tabs and a prescription for a glucagon emergency kit. A lab slip for stat labs including glucose, insulin, C-peptide, thyroid-stimulating hormone (TSH), prolactin, adrenocorticotropic hormone (ACTH), cortisol, and comprehensive metabolic panel was given to her and she was instructed to have the lab work done immediately during or after experiencing a hypoglycemic episode. Within one week, she had another symptomatic hypoglycemic episode, a fingerstick glucose reading was in the 50s, and she went to the laboratory. Results demonstrated a serum glucose of 66 mg/dL, insulin 4.4 μU/mL (normal 1-21 μU/mL), and C-peptide 3.7 ng/mL (normal 1-5.2 ng/mL). TSH, prolactin, ACTH, cortisol, liver function tests, creatinine, and electrolytes were all normal. A magnetic resonance imaging (MRI)

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scan of the pituitary gland and pancreas with and without contrast were normal.

Patient course

She continued to have frequent hypoglycemic episodes for the next two weeks and was admitted to the hospital for a supervised 72-hour fast. On the second day of the fast, she awoke at 5:00 AM disoriented, confused, and sweating. Her blood glucose was 38 mg/dL, insulin was 3.9 μU/mL, proinsulin was 36 pg/mL (normal 3-20 pg/mL), and C-peptide was 6.1 ng/mL. Drug screens for sulfonylurea and repaglinide were negative. Because of the witnessed hypoglycemia under observation, further imaging was ordered. An endoscopic ultrasound demonstrated an enhancing heterogeneous 9.5-mm mass in the pancreatic tail, suggestive of an insulinoma.

She was prescribed diazoxide while awaiting evaluation by a neuroendocrine surgeon but continued to have frequent symptomatic hypoglycemic episodes. She subsequently underwent a spleen-sparing distal pancreatectomy with complete resection of the mass. Pathology confirmed a well differentiated insulin-secreting neuroendocrine neoplasm with no evidence of invasion or malignant features. Postoperatively, she has done very well, with complete resolution of her symptoms. She followed up with her endocrinologist two months postoperatively and had lost 20 lbs and was feeling well. She had no further episodes of hypoglycemia.

Topic review

Insulinomas are rare endocrine islet cell tumors that ectopically secrete insulin in a random and inappropriate pattern, resulting in spontaneous hypoglycemia. They are the most common functional pancreatic neuroendocrine tumors and the most common cause of hypoglycemia resulting from endogenous hyperinsulinism.[1-3] The estimated incidence is 1 case per 250,000 patient-years.[1] The majority of insulinomas are benign (90%), sporadic (90%), solitary (90%), small (90% are >2 cm and 40% are <1 cm), hypervascular, and equally distributed throughout the pancreatic head, body, and tail.[1,3,4] Approximately 10% are multiple, 10% are malignant, and 10% are familial, which are all associated with MEN-1 (5-10% of all insulinoma cases).[1-4] They are more common in women (2:1) and usually occur in the fifth or sixth decade of life. When an insulinoma is part of MEN-1, they are found more commonly in the third decade.[3-5]

Insulinomas should always be suspected in a healthy person presenting with spontaneous hypoglycemia, especially if they occur at night, after fasting longer than 4 hours, or after exercise.[1,2,4] The diagnostic criteria for an insulinoma includes when someone without diabetes or other exacerbating condition presents with Whipple's triad (which is considered pathognomonic) and includes: (1) Symptoms of neuroglycopenia; (2) documented hypoglycemia (plasma glucose levels <50 mg/dL); and (3) relief of symptoms once the plasma glucose level is restored.[2,5] Neurogenic (or autonomic) hypoglycemic symptoms, which result from the catecholaminergic response to hypoglycemia, commonly occur with plasma glucose concentrations between 65 and 50 mg/dL and may include anxiety, tremor, nausea, hunger, sweating, palpitations, and paresthesias.[2,4-6] Neuroglycopenic symptoms are the direct result of central nervous system glucose deprivation and usually become apparent once the plasma glucose falls below 45 mg/dL.[2,5] These symptoms are more serious and may include fatigue, lethargy, headache, visual changes, behavioral changes, confusion, disorientation, amnesia, seizure, loss of consciousness, and even death if the hypoglycemia is severe and prolonged.[2,4,5] Some patients may develop hypoglycemic unawareness similar to patients with type 1 diabetes mellitus as a result of central nervous system adaptation to the chronic hypoglycemia.[7] Weight gain is common and is usually the result of an overattempt to relieve symptoms of hypoglycemia with food ingestion.[2,8]

Other causes of hypoglycemia in healthy-appearing patients should be considered and include noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), insulin- or sulfonylurea-induced factitious hypoglycemia, strenuous exercise, and ketotic hypoglycemia.[2,7] Severe liver disease, thyrotoxicosis, alcoholism, poor nutrition, or other extra pancreatic tumors should also be considered as a possible etiologies of fasting hypoglycemia.[4] It has been estimated that 20% of patients with an insulinoma are initially misdiagnosed with a psychiatric, seizure, or other neurologic disorder.[9] The mean delay between onset of continuous symptoms and diagnosis of an insulinoma is about 4 to 7 years.[4]

Diagnostic evaluation

Although the most characteristic feature of an insulinoma is fasting hypoglycemia, diagnosis cannot be made solely on the presence of hypoglycemia documented by a glucose meter measurement or on the resolution of symptoms relieved with food ingestion. The diagnosis of an insulinoma requires the demonstration of an inappropriately elevated plasma insulin level in the presence of spontaneous, symptomatic hypoglycemia. Diagnostic evaluation can include an overnight fast, an extended outpatient fast, or an inpatient 72-hour fast, which is the safest and most preferred method of evaluation.[2,4,5] The 72-hour inpatient fast involves hospitalization of the patient, as well as proper education of the nursing staff about the protocol and how to obtain the appropriate labs and treat the hypoglycemia when and if the patient does meet the criteria of a glucose level below 60 mg/dL with symptoms (many normal individuals glucose

levels can drop into the 50s without symptoms or consequences). Patients are allowed to drink calorie- and carbohydrate-free liquids, and physical activity should be encouraged. Supplies for venipuncture and an ampule of D50 should be at the bedside for rapid response when and if the patient develops symptomatic hypoglycemia. Blood glucose levels are measured every 4 to 8 hours initially, and every 1 to 2 hours when the blood glucose levels fall to 60 mg/dL.[4,5] The fast rarely takes 72 hours to complete because approximately 70% to 80% of patients develop hypoglycemia during the first 24 hours and 98% develop it by 48 hours.[2,4] If the patient becomes symptomatic at any point or if the blood glucose level falls below 45 to 55 mg/dL and the patient has symptoms of hypoglycemia, the test should be terminated and labs drawn. Labs include glucose, insulin, proinsulin, C-peptide, beta hydroxybutyrate, and sulfonylurea levels.[2,4,5] Autoantibodies to insulin should be measured as part of the initial evaluation when ruling out other causes of hypoglycemia but are not required at the time of hypoglycemia.[5] If symptomatic hypoglycemia does not occur, the fast should be continued for the full 72 hours. Once the labs are drawn, refeeding, an ampule of D50 IV, or 1 mg of intravenous or subcutaneous glucagon can be given and blood glucose levels should be measured after 10, 20, and 30 minutes.[2,10] Biochemical diagnosis of an insulinoma can be established when the following criteria are met: (1) Blood glucose levels below 45 to 55 mg/dL with hypoglycemic symptoms; (2) inappropriately high insulin levels ($\geq$3 U/mL or $\geq$18 pmol/L) and proinsulin levels ($\geq$5 pmol/L); (3) elevated C1-peptide levels ($\geq$0.6 ng/mL or $\geq$0.2 nmol/L); and (4) absence of serum sulfonylurea.[2,4,5] A high insulin and low C1-peptide suggests exogenous insulin administration.[11] A low C1 is important to exclude the presence of sulfonylurea ingestion, which can produce a biochemical profile similar to an insulinoma. Beta-hydroxybutyrate levels should be low if hyperinsulinemia is present and the measurement is often useful in cases with borderline insulin and C-peptide results.[11]

Localization of insulinomas

The recommended treatment for an insulinoma is complete surgical resection of the tumor. This is curative in the majority of the cases without benign pathology.[7,12] Although not required for diagnosis, preoperative localization with imaging optimizes the planning of a successful surgical approach.[2] Noninvasive imaging techniques including transabdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) can be helpful in detecting insulinomas.[1,2,12] MRI is superior to CT and US, especially for the detection of metastases before surgery.[7] When noninvasive techniques fail to localize a tumor, invasive techniques should be considered such as selective arteriography, transhepatic portal-venous sampling, endoscopic US (EUS), and intraoperative US (IOUS).[1-3,11] Intraoperative IOUS and careful palpation of the pancreas remain the most reliable way to localize insulinomas, with almost 100% sensitivity in the detection of tumors.[13] In addition to preoperative localization before surgery, it is also necessary to test for the presence of MEN-1 including primary hyperparathyroidism and pituitary tumors.[3]

Medical therapy aimed at preventing hypoglycemia can be used before surgery and in cases in which surgery is not done. Medications used to control blood glucose levels include diazoxide, verapamil, phenytoin, and octreotide.[3,4,8,14] The most effective drug for controlling hypoglycemia is diazoxide (50-300 mg/d with a maximum of 600 mg/d), which suppresses insulin secretion by direct action on the beta cells and by enhancing glycogenolysis. The combination of diazoxide along with small, frequent meals is most often used to control the hypoglycemia before surgery.[4,12]

Laparoscopic enucleation is the procedure of choice for all benign insulinomas, although the accuracy of this technique can only be achieved in centers with a significant case load of neuroendocrine tumors and a skilled surgeon in laparoscopic and pancreatic surgery.[2,15] Other surgical procedures such as partial distal pancreatectomy; a Whipple procedure (removal of the head of the pancreas, gastrectomy, duodenectomy, and splenectomy); and total pancreatectomy have all been reported but have higher complication rates.[2] Once the insulinoma is entirely resected and the patient is considered completely cured, periodic follow-up is important, especially for patients with malignant insulinomas and those with MEN-1. It is also important that blood glucose levels be measured frequently during hospitalization and once daily after the patient's discharge. It is not uncommon for blood glucose levels to be elevated up to 200 to 400 mg/dL for a period of several days to several weeks after surgery, and small doses of insulin should be administered in these cases.[2]

Conclusions

The evaluation of a suspected insulinoma is fairly straight forward and includes the exclusion of other endocrine causes of hypoglycemia (adrenal insufficiency, panhypopituitarism, etc.) and differentiation from fictitious hypoglycemia. The 72 hour medically supervised fast is the most appropriate diagnostic approach which can be done in any hospital if the staff is trained properly. This review should help the primary care physician understand the process and enable them to establish the diagnosis quite confidently if they wish to pursue the diagnosis themselves.

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