CME CREDIT

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Two patients with neuroglycopenia

CASE 1: A 47-YEAR-OLD MAN WITH PERIODIC 'SILLINESS'

A 47-YEAR-OLD MAN was well until approximately 2 years ago, when, according to his wife, he began to have episodes of "silliness," exhibiting unusual behavior such as roaming around the house naked with his underwear on his head. During these episodes, the patient experiences diplopia, amnesia, and hallucinations. The patient claims that he has gained approximately 40 lb within 1 year.

The patient's wife states that the attacks usually occur at approximately 5:00 PM. The episodes are sometimes precipitated by work or exercise and are relieved with food. There is no family history of diabetes. The patient takes no medications. Physical examination reveals nothing remarkable; his mental status and neurological status are normal.

CNS symptoms usually predominate in patients with insulinomas

What test is needed?

1 What is the most appropriate diagnostic test at this point?

- ❑ A computed tomographic (CT) scan of the head
- ❑ A CT scan of the abdomen
- ❑ A glucose tolerance test
- ❑ A serum glucose measurement during an episode
- ❑ Angiography
- ❑ Ultrasonography of the abdomen

This patient's symptoms suggest hypoglycemia, for which the most useful diagnostic test would be to measure the serum glucose level during an episode. Measuring the fasting glucose and insulin levels would also be valuable, to look for a low glucose level with a corresponding inappropriately increased insulin concentration.

When considering hypoglycemia as a cause of "spells" or altered behavior, it is essential to obtain a careful history of the precipitating and relieving factors. The physician should ask about the onset and duration of symptoms and their temporal relationship to drugs, emotion, meals, and exercise. Often these details will have to be supplied by family members or friends, because the patient may be amnesic about hypoglycemic events and unaware of any unusual pattern of behavior.

Autonomic and neuroglycopenic symptoms of hypoglycemia

Hypoglycemia is associated with the release of a number of counterregulatory hormones that attempt to compensate for the low glucose levels.[1] The manifestations of hypoglycemia can be physiologically divided into autonomic and neuroglycopenic symptoms.

Autonomic symptoms result from simultaneous sympathetic and parasympathetic activation of the hypothalamus; the most common are diaphoresis, tremulousness, and palpitations.

Neuroglycopenic symptoms, like those in our patient, are the direct result of glucose deprivation of the central nervous system, resulting in impaired cognitive function.[2,3] Unlike adipose, muscle, or liver tissue, the central nervous system needs a continuous supply of glucose. In response to hypoglycemia, the brain can increase its rate of glucose transport, but this compensatory mechanism may be inadequate to maintain adequate glucose concentrations in the brain if the blood glucose level is extremely low. Neuroglycopenic symptoms usually predominate in patients with insulinomas.[4,5]

Whipple's triad of symptoms for diagnosing insulinoma

In 1933, Whipple[6] proposed three criteria ("Whipple's triad") for diagnosing insulinoma:

- Spontaneous symptoms of hypoglycemia
- Documented hypoglycemia during the symptoms
- Immediate relief of symptoms by ingestion of glucose

Hyperinsulinism became another criterion after the immunoreactive radioimmunoassay for insulin was developed in 1959. During episodes of hypoglycemia, plasma insulin levels higher than 6 μU/mL and C-peptide levels higher than 0.2 nmol are consistent with hyperinsulinism.[4–7]

The classic insulin-to-glucose ratio should not be used with values measured during periods of normoglycemia. (In this ratio, insulin values are expressed in μU/mL and glucose values as mg/dL; ratios higher than 0.3 are abnormal.)

The diagnosis of hypoglycemia with hyperinsulinism should be made clinically and biochemically before performing any imaging studies. The oral glucose tolerance test has been used to evaluate patients with symptoms consistent with reactive hypoglycemia (ie, autonomic symptoms in response to a meal); however, it is usually not helpful in diagnosing hyperinsulinemic hypoglycemia (characterized by neuroglycopenic symptoms when fasting).

What is the best therapy for insulinoma?

We obtained fasting glucose and insulin levels in this patient; his serum glucose level was 39 mg/dL (normal 65–110 mg/dL) and his insulin level was 31 μU/mL (normal 4.0–24 μU/mL). A CT scan (FIGURE 1) and an angiogram (FIGURE 2) showed findings consistent with a mass in the pancreas.

2 What is the best therapy for this patient?

- ❑ Referral to a nutritionist
- ❑ Diazoxide
- ❑ Prednisone
- ❑ Propranolol
- ❑ Surgery

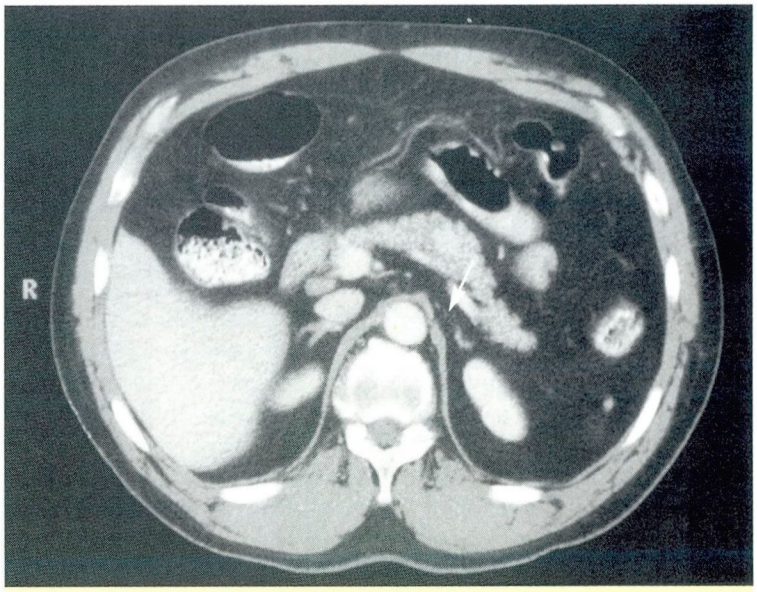

FIGURE 1. Computed tomographic scan of the pancreas. A 2.5–3.0-cm isodense focal lobulation (arrow) extends anteriorly from the pancreatic body.

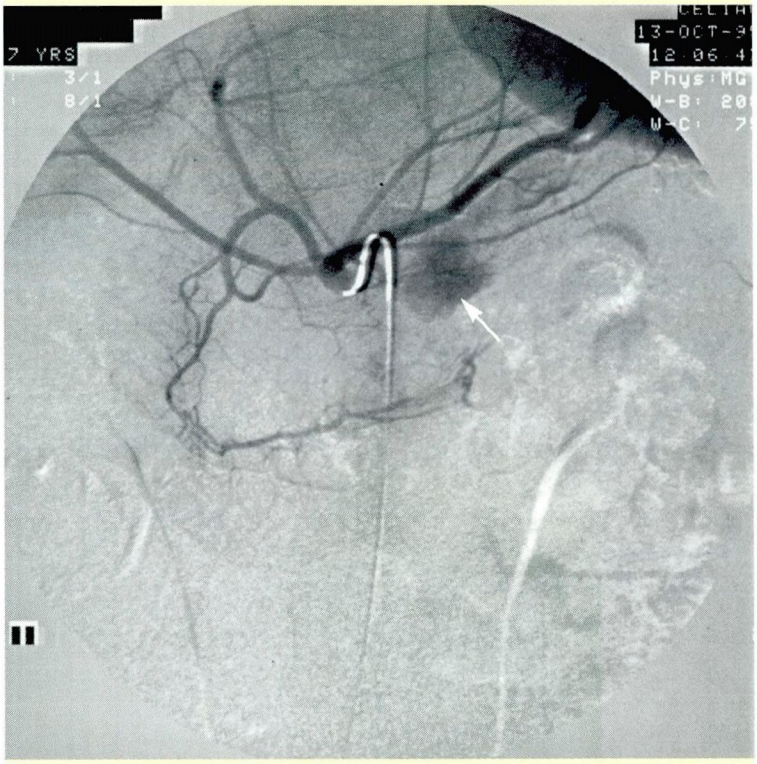

FIGURE 2. Visceral arteriography. Injection of dye into the celiac axis demonstrated a rounded hypervascular lesion (arrow) with an irregular contour in the region of the junction of the body and the tail of the pancreas.

The only curative treatment for insulin-secreting islet-cell tumors is surgery. Such surgery should not be delayed, as prolonged and repeated hypoglycemic attacks may cause permanent cerebral damage.[8] Before surgery, dietary adjustment with small frequent meals can reduce symptoms in most cases. Medical therapy with diazoxide (a nondiuretic benzothiadiazine derivative that inhibits insulin release), somatostatin analogues, verapamil, and phenytoin has been used preoperatively in severe hypoglycemia and for patients with nonresectable metastatic tumors.[9]

The patient underwent subtotal distal pancreatectomy and splenectomy. A mass measuring 3.5 × 3.5 × 3.0 cm was resected from the body of the pancreas. The pathologic findings were consistent with an insulinoma. After surgery, the symptoms did not recur.

CASE 2: A WOMAN WITH SYNCOPE

A 40-year-old white woman with a history of mitral valve prolapse was referred because of syncope for which she had been hospitalized several times in the past 3 years. Extensive neurologic and cardiac evaluations had shown no clear cause of these events. Previous diagnoses included nonepileptic seizures and major depression. While the patient was in the hospital in October 1995, she had a fingerstick capillary glucose measurement of 41 mg/dL. A CT scan of the abdomen showed some fullness in the pancreas.

The insulin-to-glucose ratio is not helpful during normoglycemia

The patient complains of episodes of tremulousness, diaphoresis, headaches, dizziness, and palpitations when she misses meals. Her weight is stable and her menses are normal. Her father had diabetes and was "on pills"; her sister had a history of a brain tumor. The patient is thin and appears anxious; physical and neurologic examination reveals nothing remarkable.

What treatment is appropriate?

3 What is your next step?

- ❑ Admit for surgery
- ❑ Obtain fasting glucose and insulin determinations
- ❑ Send patient home and tell her not to worry
- ❑ Order a nutrition consult for diet control
- ❑ Prescribe medical therapy with diazoxide

Any potentially debilitating condition needs to be confirmed before starting therapy; therefore, fasting glucose and insulin levels should be obtained. Medical or surgical therapy is not appropriate at this point. If the patient is not experiencing any symptoms during the examination, it may be necessary to provoke hypoglycemia through an overnight fast with or without exercise.

The patient fasted for 24 hours as an outpatient and experienced no hypoglycemic symptoms. Fingerstick capillary glucose levels ranged from 53 to 76 mg/dL.

4 What is your next step?

- ❑ Admit for surgery
- ❑ Admit for a 72-hour fast
- ❑ Send the patient home and tell her not to worry about it
- ❑ Send her to a dietitian
- ❑ Prescribe diazoxide

Young, healthy women may have fasting blood glucose values of less than 45 mg/dL (2.5 mmol/L) without experiencing any symptoms.[10] Fasting values between 45 and 60 mg/dL (2.5–3.3 mmol/L) are not necessarily pathologic and do not routinely need further evaluation if there are no accompanying symptoms or evidence of hyperinsulinism.[10]

How long a fast is necessary?

If an overnight or 24-hour fast does not stimulate any symptoms, the next step is a 72-hour fast—the most reliable test for evaluating hypoglycemia caused by endogenous hyperinsulinism due to an insulinoma. In a series of 51 patients with insulinomas reported by Service,[7,10] 35% developed Whipple's triad within 12 hours, 74% within 24 hours, and 92% within 48 hours. Approximately 2% of patients with insulinomas can fast for 72 or 96 hours without developing Whipple's triad. This patient's history of syncope associated

TABLE 1

Fasting glucose, insulin, and C-peptide in a patient with syncope

DATE	TIME	GLUCOSE (MG/DL)	INSULIN (MU/ML)	C-PEPTIDE (NG/ML)
6/8	13:50	76	4.0	0.9
6/8	19:50	94	5.6	1.0
6/8	23:50	33	652.0	0.5
6/9	06:00	94	—	—
6/9	13:11	44	230	0.4

Insulin antibodies: < 5%

with possible hypoglycemia necessitates further evaluation.

The patient was admitted for a 72-hour supervised fast; the results are shown in TABLE 1.

Sorting out the data

5 What is your diagnosis?

- ❑ Normal physiologic response
- ❑ Endogenous hyperinsulinism
- ❑ Exogenous hyperinsulinism
- ❑ Reactive hypoglycemia

With insulin use, insulin levels are high and C-peptide levels are low

In an otherwise-healthy patient with established hypoglycemia and progressive and recurrent neuroglycopenic symptoms, the differential diagnosis is usually insulinoma vs factitious hypoglycemia, the latter usually due to use of insulin or a sulfonylurea.

The C-peptide level and the presence of insulin antibodies can differentiate endogenous vs exogenous hyperinsulinism. C-peptide is the connecting peptide of proinsulin and is secreted in equimolar quantities with endogenous insulin.

Sulfonylurea drugs stimulate secretion of both insulin and C-peptide. Exogenous insulin does not contain C-peptide; insulin injections *suppress* secretion of endogenous insulin and C-peptide. Although most patients who inject insulin do not have insulin antibodies, the presence of such antibodies usually indicates that insulin has been given by injection.

In factitious hypoglycemia due to insulin use, plasma insulin levels are high and C-peptide levels are low; in sulfonylurea-induced hypoglycemia, insulin levels and C-peptide levels are high. In cases in which hyperinsulinism due to sulfonylureas must be distinguished from an insulinoma, the presence of sulfonylurea metabolites in the plasma or urine may be useful.

In this case, the sharp rise in insulin with a corresponding decline in C-peptide can only be consistent with exogenous insulin use. When the patient was told that her results indicated insulin use, she denied injecting insulin. She did not return for follow-up. This is a common outcome in such circumstances.

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