Case Study: Diagnostic Dilemma in a Patient With Insulinoma

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Presentation
B.Y. is a 70-year-old woman who was referred to the diabetes clinic by her primary care provider for work-up of hypoglycemia. She had known coronary artery disease and was status post-coronary artery bypass grafting. Her symptoms included fatigue and some depression. Initial laboratory testing revealed two blood glucose levels in the 30- to 40-mg/dl range. She was referred to our clinic for further evaluation.

She was asked to come in fasting. History revealed that she did, indeed, have severe fatigue. She did not complain of syncope, palpitations, or diaphoresis. She had experienced two episodes of mild dizziness with standing, but each of these had resolved spontaneously and had been short-lived. Physical exam revealed an elevated blood pressure of 194/97 mmHg. Her weight was 245 lb and had not changed recently.

Fasting serum glucose, insulin, pro-insulin, C-peptide, beta-hydroxybutyrate, sulfonylurea drug screen, thyroid function tests, somatomedin C, and a random morning cortisol level were measured. At 8:45 A.M., her blood glucose was 90 mg/dl, insulin was 22.8 μU/ml (range 2.6–24.4 μU/ml), and proinsulin was 302.6 pmol/l (range 2.1–26.8 pmol/l). However, by 4:00 P.M., her glucose was 37 mg/dl, insulin was persistently elevated at 22.2 μU/ml, and proinsulin was 280.5 pmol/l. Her C-peptide levels were slightly elevated at 3.7 ng/ml in the morning and 3.8 ng/ml in the afternoon (range 0.8–3.5 ng/ml). Random morning cortisol, thyroid-stimulating hormone, and somatomedin C were normal. Her beta-hydroxybutyrate was 2.2 mg/dl (range < 3.1 mg/dl), suggesting that overproduction of insulin was preventing formation of ketoacids despite fasting. Biochemical evidence of hypoglycemia with hyperinsulinemia led to radiological investigation for an insulinoma. Computed tomography (CT) scanning of the abdomen showed mild steatosis of the liver, benign appearing right renal cyst, and a large hiatal hernia, but no pancreatic mass. Several days later, the patient's sulfonylurea screen came back positive for tolbutamide.

Further evaluation was pursued for factitious hypoglycemia. Medication lists for both the patient and her husband were reviewed extensively along with corroboration from her primary care physician and pharmacist. A repeat sulfonylurea drug screen was ordered.

Despite very low blood glucose levels, the patient had hypoglycemia unawareness. She was encouraged to monitor her blood glucose and treat hypoglycemia with glucose tablets or other carbohydrate intake. Repeat fasting laboratory studies were performed, including all of the above tests with the exception of cortisol, thyroid-stimulating hormone, and somatomedin C, which were normal. Hypoglycemia was reproduced with a nadir of 29 mg/dl accompanied by inappropriately high C-peptide, insulin, and proinsulin levels. A repeat sulfonylurea drug screen was negative.

B.Y. continued to have hypoglycemia unawareness as evidenced by glucose meter readings frequently < 50 mg/dl unaccompanied by symptoms. She had a third fasting study and sulfonylurea screen secondary to a previous positive screen. She had a nadir glucose reading of 40 mg/dl without symptoms, and the third sulfonylurea drug screen was negative. Insulin, proinsulin, and C-peptide levels were again elevated and similar to the previous values, and beta-hydroxybutyrate was suppressed, suggesting insulinoma. Subsequently, the patient had a magnetic resonance imaging and angiogram of the abdomen, and a 1.6-cm enhancing mass was found in the head of the pancreas. Surgical excision was recommended for curative treatment. She underwent enucleation of the mass, and the surgical pathology was consistent with insulinoma.

In follow-up, the patient was found to have mild hyperglycemia, suggesting that the insulinoma may have been masking mild type 2 diabetes. Diet and exercise were considered initially.

Questions
1. What are the symptoms of hypoglycemia?
2. What is the best way to work up hypoglycemia or suspected hypoglycemia?
3. Why did the original sulfonylurea drug screen come back positive?
4. What is the best imaging modality for diagnosis of insulinoma?

Commentary
Symptoms of hypoglycemia can be classified into two categories: autonomic and neuroglycopenic. The autonomic symptoms typically include sweating, trembling, anxiety, hot flashes, and nausea. Neuroglycopenic symptoms...
include dizziness, confusion, tiredness, difficulty speaking, headache, and poor concentration.\(^1\)

Symptoms of hypoglycemia can become blunted with repeated episodes.\(^1\) For this reason, many patients with insulinoma gradually develop hypoglycemia unawareness. Mitrakou et al.\(^2\) have described lower scores for autonomic and neuroglycopenic symptoms in patients with insulinoma compared with normal subjects matched for age, weight, and sex. Further, this group showed that the counterregulatory hormonal responses (plasma epinephrine, norepinephrine, glucagon, growth hormone, and cortisol) were lower than in the normal subjects.\(^2\) However, after surgical removal of insulinoma, the patients no longer had statistically significant differences in their neuroglycopenic or counterregulatory responses, suggesting reversibility of this deficit.\(^2\)

Hypoglycemia is a fairly frequent reason for referral, but insulinoma is rare, with an estimated incidence of four per 1 million, making clinical suspicion extremely important in diagnosis.\(^3\) Possible etiologies for hypoglycemia include insulinoma, laboratory error, reactive hypoglycemia, hypothyroidism, adrenal insufficiency, growth hormone deficiency, or use of oral hypoglycemic agents or insulin. The biochemical hallmark of this diagnosis is fasting hypoglycemia with simultaneous inappropriately elevated insulin levels. Classically, 72-hour fasts are performed. However, outpatient fasts can provide the required data and be much more cost-effective than inpatient fasts.

Table 1 and 2 are protocols for a 72-hour fasting test and how to interpret their results.\(^1\)

In B.Y., insulin, proinsulin, and C-peptide levels were all elevated despite hypoglycemia, suggesting insulinoma.

The false-positive initial sulfonylurea drug screen raises another pertinent question in terms of how to distinguish factitious hypoglycemia. Magni et al.\(^4\) have published findings of false-positives for sulfonylurea testing using high-pressure liquid chromatography (HPLC) with ultraviolet or fluorescence as compared to mass spectrometry, which is a more reliable method of detection of a particular drug. Our laboratory uses HPLC. Repeat testing can be helpful, and in our case two subsequent tests showed no evidence of sulfonylurea. It is important to confirm that the laboratory processing this test checks for most commonly prescribed sulfonylureas because not all laboratories do this routinely.

In addition to the biochemical assays involved in diagnosing insulinomas, imaging remains a critical part of diagnosis. The best imaging modality to be coupled with the biochemical work-up is debatable. Many simply use preoperative transabdominal ultrasound and report up to nearly a two-thirds success rate in localizing insulinomas preoperatively.\(^5\) However, other groups have reported much lower success rates, and it is certainly agreed to be operator dependent.

Intraoperative ultrasonography is now touted as the imaging study of choice for its anatomical precision advantage over preoperative transabdominal ultrasound, but many surgeons prefer to know the location of the tumor before surgery. Endoscopic ultrasound was reported in one study\(^6\) to have up to a 93% sensitivity and is certainly attractive with its relative noninvasiveness and superior anatomical precision compared with transabdominal ultrasound. Availability and operator dependence remain drawbacks.\(^6\)

Octreotide scan combined with single-photon emission CT yields results especially helpful in the setting of distant metastases because of its advantage of whole body imaging.\(^7\) CT scanning is cheap, available, and noninvasive and has been enhanced with the development of helical CTs. However, the diagnostic yield is very dependent on the size of the tumor, with small tumors still difficult to localize.\(^6\) Magnetic resonance imaging and angiogram have been shown to be quite effective, with sensitivity of 85% and specificity of 100% in one series.\(^3\) Other imaging and localization modalities include arteriography, transhepatic portal venous sampling, and selective arterial calcium stimulation with venous sampling.

Invasiveness, risk, and cost become factors with all of these modalities, as does availability. Practitioners should take into account local expertise, availability, and cost, as well as patient and surgeon preferences and start with CT scanning or transabdominal ultrasound and move towards more invasive and expensive tests as needed. With our patient, magnetic resonance was successful in locating the lesion when CT was less invasive than other modalities.

### Table 1. Protocol for 72-Hour Fast

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tr>
<td>1.</td>
<td>Date the onset of the fast as of the last ingestion of calories. Discontinue all nonessential medications.</td>
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<tr>
<td>2.</td>
<td>Allow the patient to drink calorie-free and caffeine-free beverages.</td>
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<td>3.</td>
<td>Ensure that the patient is active during waking hours.</td>
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<td>4.</td>
<td>Measure the levels of plasma glucose, insulin, C-peptide, and proinsulin in the same specimen; repeat measurements every 6 hours until plasma glucose is ≤ 60 mg per deciliter, when the interval should be reduced to every 1–2 hours.</td>
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<tr>
<td>5.</td>
<td>End the fast when the plasma glucose level is ≤ 45 mg/dl (2.5 mmol per liter) and the patient has symptoms or signs of hypoglycemia.</td>
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<tr>
<td>6.</td>
<td>At the end of the fast, measure the plasma levels of glucose, insulin, C-peptide, proinsulin, beta-hydroxybutyrate, and sulfonylurea in the same specimen; then inject 1 mg glucagon intravenously and measure the plasma glucose level after 10, 20, and 30 minutes. Then feed the patient.</td>
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<tr>
<td>7.</td>
<td>When a deficiency is suspected, measure the plasma cortisol, growth hormone, or glucagon at the beginning and end of the fast.</td>
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Clinical Pearls

- Insulinoma remains a rare entity with sometimes misleading absence of classic neuroglycopenic symptoms. Index of suspicion must be high to reach the correct diagnosis.
- Detailed biochemical investigation should be pursued to prove the diagnosis and rule out secondary causes.
- Appropriate radiological testing options should be considered based on sensitivity and specificity because insulinomas can be extremely small and difficult to localize.

Table 2. Diagnostic Interpretation of the Results of a 72-Hour Fast*

| Diagnosis                                      | Symptoms or signs | Glucose† mg/dl | Insulin‡§ µU/ml | C-peptide¶§ nmol/l | Proinsulin|||| nmol/l | Beta-hydroxybutyrate mmol/l | Change in glucose** mg/dl | Sulfonylurea in plasma |
|-----------------------------------------------|------------------|----------------|-----------------|-------------------|----------------|-----------------------------|--------------------------|------------------------|
| Normal                                        | No               | ≥ 40           | < 6             | < 0.2             | < 5            | > 2.7                       | < 25                     | No                     |
| Insulinoma                                    | Yes              | ≤ 45           | ≥ 6††           | ≥ 0.2             | ≥ 5            | ≤ 2.7                       | ≥ 25                     | No                     |
| Factitious hypoglycemia from insulin          | Yes              | ≤ 45           | ≥ 6‡‡           | < 0.2             | < 5            | ≥ 2.7                       | ≥ 25                     | No                     |
| Sulfonylurea-induced hypoglycemia             | Yes              | ≤ 45           | ≥ 6‡‡           | < 0.2             | < 5            | ≥ 2.7                       | ≥ 25                     | Yes§§                  |
| Hypoglycemia mediated by insulin-like growth factor | Yes             | ≤ 45           | ≤ 6             | < 0.2             | < 5            | ≤ 2.7                       | ≥ 25                     | No                     |
| Non–insulin-mediated hypoglycemia             | Yes              | ≤ 45           | < 6             | < 0.2             | < 5            | > 2.7                       | < 25                     | No                     |
| Inadvertent feeding during the fast           | No               | ≥ 45           | < 6             | < 0.2             | < 5            | ≤ 2.7                       | ≥ 25                     | No                     |
| Nonhypoglycemic disorder                      | Yes              | ≥ 40           | < 6             | < 0.2             | < 5            | > 2.7                       | < 25                     | No                     |

*Measurements are made at the point the decision is made to fast.
†Sequential plasma glucose measurements in the hypoglycemic range fluctuate. Plasma glucose levels ≤ 45 mg/dl at the time a decision is made to end the fast may rise to as much as 56 mg/dl when the fast is actually ended ~1 hour later. Plasma glucose levels may be as low as 40 mg/dl during prolonged fasting in normal women.
‡‡Plasma insulin levels may be very high (>100 µU/ml or >1,000 µU/ml) in factitious hypoglycemia from insulin.
††Ratios of insulin to glucose are of no diagnostic value in patients with insulinomas.
**In response to intravenous glucagon (peak value minus value at end of fast). To convert values to millimoles per liter, multiply by 0.05551.
¶Measured by the immunochemiluminometric technique (lower limit of detection, 0.2 pmol/l).
|| Measured by the immunochemiluminometric technique (lower limit of detection, 0.033 nmol/l).
‡‡‡Plasma insulin levels may be very high (>100 µU/ml or >1,000 µU/ml) in factitious hypoglycemia from insulin.
§§Unlike the first generation of sulfonylurea drugs, which were easily measured, second-generation drugs are not.

REFERENCES

5Grant C: Insulinoma. Best Pract Res Clin Gastroenterol 19:783–789, 2005

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