CLINICAL VIGNETTE

New Onset Hypoglycemia in a Patient

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Case Presentation

A 65-year-old Caucasian female was complaining of shaking and sweating after meals to her primary care physician. As part of her work up, a 3-hour oral glucose (75gm load) tolerance test was ordered. The following were her results:

Timing	Glucose (mg/ld.)	Insulin (uIU/mL)
Fasting	88	8.4
1 hour	174	Not processed
2 hour	36	Not processed
3 hour	50	3.9

The patient was referred to endocrinology in response to these labs. She was in her usual state of good health up until about nine months ago when she started to notice mild sweats and tremors occasionally after meals. The symptoms became more prominent and frequent over the next seven months. By the time she sought medical attention, she was having profuse sweats, tremors, and severe fatigue after most meals. There was no associated abdominal pain, bloating, or diarrhea.

These symptoms would occur usually within one hour of eating and were self-limited. Sometimes eating would improve the symptoms. She was never awakened with these symptoms in the middle of the night and was able to provide fasting labs without any similar episodes.

Upon review of her diet, she felt that the symptoms were more prominent after eating relatively larger meals, which would often consist of pastas or rice.

Review of systems revealed that, one month prior, she had a near-syncopal episode after a particularly large meal. She denied actually losing consciousness and did not notice any weakness, slurred speech, or severe headache. She did not go to the emergency room and, instead, waited for her symptoms to improve, which they did over the course of a few hours. She had no such episodes thereafter. She also reported recent weight gain, which she attributed to having to eat more to keep her sugars up. The rest of the review was unremarkable.

In discussing her past medical history, the patient reported being told that she had 'pre-diabetes' about five years ago and was recommended to make lifestyle changes. She was never given anti-hyperglycemic medication. She was overweight at the time and decided to pursue gastric bypass surgery and successfully underwent a Roux-en-Y procedure. Over the course of a year, she lost sixty pounds and reported that her blood sugars had normalized. The rest of her medical history included hypothyroidism, anemia, depression with anxiety, and gastric reflux. Her father had coronary artery disease, and her mother had breast cancer. No one in her family had diabetes, and she did not recall anyone complaining of hypoglycemia.

The patient's chronic medications were buspirone, citalopram, pantoprazole, and Armour thyroid. Outside of vitamin E, she denied taking any other vitamins, supplements, or herbal preparations.

On examination, the patient's blood pressure was 122/76 mmHg with a resting pulse of 64/minute. Her weight was 226 pounds with a height of 66 inches with BMI of 36.5. She did not appear ill. She did not have Cushingnoid features and was not hirsute. Her thyroid was normal size with no palpable masses. The rest of her exam was unremarkable. In addition to her oral glucose tolerance test (OGTT), her A1c was 5.7%. She was not anemic; calcium and vitamin D levels were normal as were the liver function tests and thyroid labs. Insulin antibodies were negative. A panel for hypoglycemic agents was negative. AM cortisol level was 12.

Of note, the patient reported having mild tremors and sweats toward the second hour of her OGTT with the symptoms significantly worsening by the time the test was completed.

She was suspected of having either post-prandial hypoglycemia due to her gastric bypass surgery or an insulinoma (her insulin levels were high in relation to her hypoglycemia on the OGTT). She was recommended to repeat labs after a large meal in an attempt to replicate her post-prandial symptoms. She refused stating that she was afraid of having another episode. Instead, she agreed to a 72-hour fast to rule out an insulin producing tumor.

The inpatient stay was uneventful with the glucose levels never falling below 62 mg/dL. Refeeding at the hospital did not trigger any symptoms. Further testing, including a supervised meal challenge, was refused as the patient was getting frustrated with lack of findings. Further testing was deferred, and she started dietary modifications that included smaller, frequent meals consisting of complex high-fiber carbohydrates, more proteins, and healthier fats. Given her A1c of 5.7% and history of abnormal glucoses, she was also started on metformin 500mg twice a day. The patient agreed to resume testing if her symptoms did not improve.

At her two month follow-up visit, the patient was happy to report that her symptoms had become infrequent. She was following the outlined diet plan and medical regimen. The diagnosis was changed from post-prandial hypoglycemia to dumping syndrome (related to her gastric bypass), which was managed with dietary modification.

Discussion

The following discussion of hypoglycemia pertains to individuals without diabetes who present in an outpatient setting. A low glucose is a concerning finding but does not establish a hypoglycemic disorder. "Reactive hypoglycemia" is often used in clinical practice, but it is not a diagnosis, just a description of low sugars generally four hours post meal. Healthy people have been found with low glucose on fasting labs without having symptoms. Further testing is necessary but only when the patient satisfies all three criteria for Whipple's triad which include:

1. Symptoms that are consistent with hypoglycemia, such as tremors, sweats, hunger, and/or altered levels of consciousness;
2. Documentation of a low plasma glucose (usually below 60 mg/dL); and
3. Improvement of hypoglycemic symptoms once plasma glucose is increased.

Hypoglycemia can occur in malnourished patients due to glycogen depletion in the liver. This can be seen in long-term abusers of alcohol with inadequate nutrition. Hypoglycemia has also been reported in patients with anorexia nervosa.[1] Malnourishment usually can be detected at the time of the initial patient visit.

Adrenal insufficiency is another cause of hypoglycemia and should be suspected in those patients who present with classic symptoms of low blood pressure and fatigue – especially if they have hyponatremia.

Non-islet cell cancers can cause hypoglycemia either by high tumor burden in the liver (thereby depleting glycogen) or tumoral production of insulin-like growth factor-2 (IGF-2), which activates insulin receptor and results in glucose utilization.[2] Such patients usually present with weight loss and appear ill on general assessment.

Endogenous over-production of insulin results in hypoglycemia because the insulin levels do not appropriately decrease in the setting of falling plasma glucose. This can be seen in the following settings:

1. Insulin-producing tumors within the pancreas (insulinoma) usually present as hypoglycemia after prolonged fasts. Although some patients may also have low glucose post-meals, it is unusual for them not to have fasting hypoglycemia. Patients will often complain of weight gain due to frequently eating to maintain glucose levels.
2. Antibodies against insulin can produce hypoglycemia fasting or after a meal. Insulin produced in response to food will bind to the antibodies and then disassociate in an unregulated manner thereby increase circulating levels of insulin. Insulin antibodies should be tested in anyone with confirmed post-prandial hypoglycemia.
3. Nesidioblastosis is a histologic term used to describe beta cell hypertrophy. It can occur as a separate entity but has also been noted to occur in patients who have had Roux-en-Y gastric bypass. Why this process occurs is not completely understood. During a laboratory work up, nesidioblastosis is difficult to distinguish from insulinomas. With nesidioblastosis, the symptoms of hypoglycemia occur post-prandially as opposed to insulinomas with fasting hypoglycemia.
4. Patients' surreptitious use of either insulin or oral hypoglycemic medications must be considered when evaluating hypoglycemia – especially if testing does not find a source.

Once a patient has met criteria for Whipple's triad the following tests are needed during a hypoglycemic episode:

1. Glucose.
2. Insulin. Measurements of plasma insulin cannot distinguish between endogenous and exogenous sources.
3. C-peptide. C-peptide is a byproduct of endogenous insulin production.
4. Proinsulin. Proinsulin is a precursor to endogenous insulin.
5. Beta-hydroxybutyrate (BHOB). BHOB is a ketone and, since insulin lowers ketone production, BHOB should be low in presence of insulin (both endogenous and exogenous).
6. Screening panel for hypoglycemic agents.

Insulin antibodies should also be tested but do not need to be drawn during a hypoglycemic episode.

Since most episodes of hypoglycemia are unwitnessed in the outpatient setting, testing needs to be done in a fashion that would replicate the patients' timing of symptoms. So, for example, a patient who is having symptoms after a prolonged fast, post-meal testing would be not as useful. The exception to this would be if there was a suspicion for an insulinoma, in which case patients may suffer both fasting (mostly) and post-prandial hypoglycemia.

For those patients with fasting symptoms, a 72-hour fast is considered the best approach. This is usually done in the inpatient setting with labs (glucose, insulin, C-peptide, proinsulin, and BHOB) being drawn every six hours until the blood sugars drop below 60 mg/dL. After this point, labs are drawn every hour. The test is concluded when plasma glucose levels are less than 45 mg/dL, symptoms of hypoglycemia occur, or when the 72 hours are over. Once the test is over, patients are often given 1 mg of glucagon with glucose levels drawn 20 and 30 minutes after. This part of the test takes into account that insulin will increase glycogen in the liver. Glycogen is usually depleted after a prolonged fast. As such, for those exposed to high amounts of insulin, there should be some glycogen stores despite the fasting thereby causing a rise in glucose when exposed to glucagon, which causes glycolysis.

In turn, patients without excess insulin will not have a significant rise in glucose (< 25 mg/dL) when given glucagon. A screening panel for hypoglycemic agents should also be drawn at the conclusion of the test. Patients who develop hypoglycemia (glucose < 50 mg/dL) should have their results interpreted as follows:

1. Insulin levels should drop (below 3 uIU/mL) when plasma glucose levels are below 50 mg/dL. Insulin will remain elevated in patients with insulinomas, nesidioblastosis, insulin antibodies, hypoglycemic agents, or exogenous use of insulin. In the setting of non-islet cell cancers, insulin levels will be low due to hypoglycemia being mediated by other factors (e.g., IGF-2).
2. C-peptide levels will be high (over 0.6 ng/mL) when endogenous insulin is in excess as in insulinomas, nesidioblastosis, or use of hypoglycemic agents. C-peptide levels are useful in distinguishing surreptitious use of insulin, when they will be low in the setting of high insulin levels. Non-islet cell cancers will have low C-peptide levels for the same reasons.
3. Proinsulin levels can help when the C-peptide levels are borderline. Since it is a precursor to insulin, proinsulin will be high when endogenous insulin levels are high.
4. BHOB are low (below 2.7 mmol/L) with excessive insulin as opposed to being higher in normal patients.

It is difficult to isolate the cause of hypoglycemia with a 72-hr fast, hence the importance of a thorough history and physical to help put the results into context.

For patients having hypoglycemic symptoms after meals, a postprandial assessment should be made. An OGTT would be a logical next choice as it is easy to order and administer. However, studies have shown that the OGTT is not accurate for three reasons:[3]

1. Normal patients can have glucose levels drop to less than 50 ng/mL during prolonged OGTT testing;
2. Patients have reported hypoglycemic symptoms when given a placebo rather than glucose; and
3. No direct correlation between symptoms and sugars has been shown on OGTT.

Given these limitations, it is preferred to use a mixed meal challenge, in which patients eat solid and liquid foods in an attempt to induce hypoglycemic symptoms. The primary goal of such testing is to document Whipple's triad. Testing is done in the office with labs (glucose, insulin, C-peptide, proinsulin) drawn every thirty minutes for up to five hours. A screening panel for hypoglycemic agents is drawn at the end of the test. Testing is complete either when the patient develops hypoglycemic symptoms or when the five hours are reached. Interpretation of the results are similar to that of the 72-hour fast. Postprandial hypoglycemia is more commonly seen in patients with nesidioblastosis, insulin antibodies, or factitious use of diabetes-related medication.[4]

Special attention is needed in patients with history of Roux-en-Y gastric bypass surgery. These patients may be experiencing dumping syndrome instead of hypoglycemia. Dumping syndrome manifests as postprandial shakes, sweats, weakness, and/or palpitations. It can be accompanied by abdominal discomfort, bloating, or diarrhea. Dumping syndrome usually follows high carbohydrate meals. Symptoms mostly occur 30 to 45 minutes after eating and are not associated with low glucose levels. Dumping syndrome is managed by having patients eat smaller portions more frequently and avoiding large intake of carbohydrates. To make things more confusing, there are case reports of nesidioblastosis developing after Roux-en-Y surgery.[5] These patients will develop low plasma glucose levels after meals but usually two to four hours after. Histologic evaluation of these patients' pancreas glands shows islet cell hypertrophy.

The proper treatment plan is developed once a diagnosis is suspected. If an insulinoma is on the top of the differential list, imaging should be pursued in an attempt to localize the tumor with the intentions of surgical correction. For those patients with postprandial hypoglycemia due to nesidioblastosis (spontaneous or related to Roux-en-Y) or insulin antibodies, medical management is an option if symptoms are mild to moderate. Options such as verapamil, octreotide, acarbose (blocks intestinal glucose uptake), or diazoxide (inhibits insulin release) are viable options. However, these medications are not without side effects, in particular acarbose and octreotide can have severe gastrointestinal effects, while diazoxide is associated with hirsutism and sodium retention. Also patients are advised to eat frequent small meals with a focus on avoiding carbohydrate intake without accompanied proteins or fat. For those patients with more severe symptoms, such as frequent bouts of altered mental status, partial or near-total pancreatectomy may be considered.

Hypoglycemia is a complex diagnosis to pinpoint and requires a careful history and physical examination. Testing should be pursued in an attempt to complete Whipple's triad. Once this is done, further evaluation is directed by clinical suspicions.

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Submitted October 11, 2016