

# Episode 61

## Problem Representation

An 80-year old man with insulin-dependent diabetes mellitus and benign prostatic hyperplasia presented with acutely altered mental status and was found to have hypoglycemia, pyuria, and an acute kidney injury.

## Schemas

The CPSEr's schema for hypoglycemia distinguishes between insulin- and noninsulin-mediated causes. Insulin-mediated hypoglycemia is most commonly an adverse effect of antihyperglycemic therapy or, rarely, endogenous insulin production. Noninsulin-mediated etiologies are driven by decreased serum glucose availability, endocrinopathies, or medications.

## Diagnosis

The constellation of his encephalopathy, objective hypoglycemia, and prompt resolution following administration of IV glucose fulfilled Whipple's Triad, confirming that hypoglycemia was responsible for his symptoms. Further laboratory workup was notable for a urinary tract infection leading to urinary retention and AKI, suggesting that his symptomatic hypoglycemia was caused by decreased clearance of exogenous insulin.

## Teaching Points

- Endogenous causes of insulin-mediated hypoglycemia are uncommon, but should particularly be considered in very symptomatic, non-diabetic patients. Endogenous insulin production<sup>1</sup> can be confirmed by inappropriately elevated insulin, C-peptide, and proinsulin levels during hypoglycemia, with no or minimal ketone body formation. Abdominal imaging is only indicated to evaluate for endogenous insulin-mediated causes (e.g., insulinoma) if testing for autoantibodies and antihyperglycemic medications are negative in a patient with documented hyperinsulinemic hypoglycemia.
- Patients with long-standing diabetes become reliant on sympathoadrenal activation during episodes of hypoglycemia, producing symptoms of tremor, sweating, palpitations, and anxiety. With recurrent hypoglycemia, the sympathetic nervous system adapts by lowering the threshold at which it responds to low blood glucose, leading to an impaired response called hypoglycemia-associated autonomic failure<sup>2</sup>. This can result in a phenomenon called hypoglycemia unawareness<sup>3</sup>, where the onset of neuroglycopenia (i.e., low glucose in the brain) precedes the autonomic response symptoms, putting patients at risk for seizures, coma, and death.
- The Warburg Effect<sup>4</sup> is an uncommon cause of hypoglycemia seen in patients with cancer and is often accompanied by lactic acidosis. The oncogenic switch that occurs in the Warburg effect alters cellular metabolism by prioritizing aerobic glycolysis over oxidative phosphorylation. As a result, cells preferentially generate large amounts of lactate. Although this yields less ATP than conventional oxidative phosphorylation, it is thought that the metabolic intermediates produced in the glycolytic pathway may be necessary precursors for cancer cell proliferation.

## Clinical Reasoning Pearl

Reza discussed a medical error he made as a resident. Making mistakes is an inevitable part of learning and practicing medicine. While these are often emotionally challenging moments, they are important opportunities for us to grow as clinicians.

### For example:

Following his mistake, Reza reevaluated all of his decisions and asked for guidance from more experienced clinicians. As he so perfectly states, "the only mistake is not learning from your mistakes."

## References

1. Cryer PE et al. Endocrine Society. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009 Mar;94(3):709-28.
2. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med.* 2013 Jul 25;369(4):362-72.
3. Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. *World J Diabetes.* 2015 Jul 10;6(7):912-26.
4. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science.* 2009 May 22;324(5930):1029-33.