An 81-year-old Mediterranean man presented to the emergency department with 6 months of episodic nervousness, warmth, sweating, and hunger that would subsequently progress to weakness, fatigue, difficulty concentrating, and “feeling shaky.” He denied loss of consciousness, dizziness, palpitations, chest pain, dyspnea, and post-event weakness. Symptoms occurred throughout the day and night and resolved by consuming snacks or juice. The patient thus consumed frequent scheduled meals throughout the day and night. He lived alone, but symptoms had been observed and confirmed by nearby family members. He was otherwise healthy and denied alcohol or drug use. His only medication was atorvastatin, and he denied use of any over-the-counter supplements or difficulty taking his medication. He had no known significant medical history aside from resection of a benign lung mass 30 years earlier. He denied other surgical history, including weight-loss surgeries. He denied personal or family history of cancer, diabetes, or endocrine disorders.

Upon initial presentation, the patient’s temperature was 36.7 ºC, heart rate 92, blood pressure 129/67 mm Hg, and oxygen saturation 99% on room air. There was no evidence of orthostatic hypotension. He was alert and oriented. His mouth appeared moist. His neck was supple, and there were no palpable lymph nodes. Heart rate and rhythm were normal and without murmurs. Lung sounds were clear bilaterally, and breathing appeared unlabored. His abdomen was soft, nontender, and without palpable masses. Neurologic examination results were unremarkable, with no cranial nerve abnormalities. He had normal strength, coordination, and gait, without tremors.

1. Taking into consideration the extensive history and careful physical examination, which test would readily point toward the most likely diagnosis during an active “spell” episode?
   a) Basic metabolic panel
   b) Electrocardiogram (ECG)
   c) Electroencephalography (EEG)
   d) Plasma fractionated metanephrines
   e) Point of care (POC) glucose check

The differential diagnosis for episodic “spells” is extremely broad, including neurologic, cardiovascular, endocrine, psychiatric, and pharmacologic etiologies, among others. To avoid an extensive diagnostic work-up, testing should focus on diagnoses with high pretest probability, based on a comprehensive history and physical examination. In this patient with no reported orthostasis, dizziness, or palpitations, common causes for spells such as orthostatic hypotension, benign paroxysmal positional vertigo, and cardiac dysrhythmia are less likely. In elderly patients, careful medication reconciliation is important, with attention to medication dosage; timing; and screening for polypharmacy, drug–drug interactions, or drug overdoses. A social screening is indicated, as a recent move, unfamiliar environment, abuse, or malnutrition could cause or exacerbate such spells.

A basic metabolic panel would identify electrolyte abnormalities, which could lead to altered mental status or arrhythmia; however, the patient had no risk factors for this. Obtaining an ECG could identify arrhythmias that might lead to near-syncpe or weakness, but arrhythmias would be unlikely in this patient with no palpitations or cardiac history. An EEG would detect partial or complex seizures that can present as spells, but patient’s symptoms lacking postictal symptoms, loss
of consciousness, and normal neurologic examination results make seizures unlikely. The patient’s autonomic symptoms could be caused by an endocrine tumor that secretes plasma catecholamines or metanephrines. But the lack of associated hypertension, palpitations, or headache argues against this diagnosis. This patient’s symptoms of profound weakness, shakiness, cognitive difficulty, and fatigue with resolution following ingestion of a carbohydrate-rich snack are highly suggestive of neuroglycopenia. The autonomic and neuroglycopenic symptoms can be attributed to hypoglycemia if low plasma glucose is confirmed. A POC glucose test obtained while the patient is symptomatic is the most appropriate rapid initial test. If low, it should be followed immediately with a venous blood sample to confirm low plasma glucose, as POC glucometers’ accuracy can be low with hypoglycemia, hypoxemia, and extreme temperature.1

In the case of our patient, glucose testing confirmed that symptoms coincided with a plasma glucose level below 60 mg/dL. The patient’s symptoms resolved once blood glucose normalized after eating. The patient was admitted to the hospital for further work-up and management of hypoglycemia. Results of laboratory testing, including complete blood count and renal and hepatic function panel, were normal.

2. Given the patient’s presentation, what is the one most likely cause for his hypoglycemia?
   a) Adrenal insufficiency
   b) Exogenous insulin administration
   c) Endogenous hyperinsulinism
   d) Medication-induced hypoglycemia
   e) Insulin autoimmune hypoglycemia syndrome

   The most common causes for hypoglycemia requiring hospitalization—including severe liver or kidney disease, sepsis, alcoholism, severe malnutrition or anorexia nervosa—were easily ruled out in our patient.2

   Rarely, adrenal insufficiency causes hypoglycemia, often related to the loss of the gluconeogenic effects of cortisol.3 However, this diagnosis would be unlikely in this patient who had no history of prolonged steroid use and no other metabolic abnormalities, hypotension, or orthostatic issues. The patient’s symptoms were consistent with the Whipple Triad: symptomatic hypoglycemia, coinciding with low serum glucose, resolving following ingestion of glucose. This suggests insulin excess, which could be from exogenous insulin administration vs endogenous insulin hypersecretion. Although surreptitious administration of insulin could be considered, this patient has no personal or family history of diabetes and would unlikely have access to insulin. Medication-induced hypoglycemia is common, and accidental or surreptitious use of such medications needs to be considered and ruled out. Our patient denied taking any drugs associated with hypoglycemia. Insulin-autoimmune hypoglycemia syndrome occurs in patients of Asian descent with underlying autoimmune disease.

   To clarify the cause of hypoglycemia, the patient underwent testing for oral hypoglycemic agents, such as sulfonylureas (not detected), insulin antibodies (negative), and insulin-like growth factor 2 (IGF2) levels 405 ng/mL (267 to 616 ng/mL), which were all negative or within normal limits. As he did not reach a plasma glucose level below 55 mg/dL during initial evaluation, he then underwent a supervised fasting test. Once his plasma glucose level reached 60 mg/dL (70 to 140 mg/dL), hourly plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate were measured. The fast ended when the patient had hypoglycemia-related symptoms and plasma glucose level was below 45 mg/dL. At this time, these laboratory results were recollected, and intravenous glucagon was administrated, with plasma glucose being measured 10, 20, and 30 minutes later. A fast lasting up to 72 hours will detect 100% of patients with inappropriate insulin secretion.3

3. At the end of the fasting study, which laboratory finding would be most consistent with endogenous insulin hypersecretion?
   a) Elevated β-hydroxybutyrate
   b) Minimal rise in blood glucose after administration of glucagon
c) Elevated insulin levels and decreased C-peptide and proinsulin levels

d) Low levels of insulin, C-peptide, and proinsulin

e) Elevated or inappropriately normal insulin, proinsulin, and C-peptide levels

In patients with excess insulin secretion, β-hydroxybutyrate levels are low because insulin is an antiketogenic compound. A poor response to glucagon after fasting would be consistent with starvation or anorexia. Such patients, who have a normally functioning pancreas, would deplete their glycogen stores by the end of a fast and would thus be unable to produce a robust response to glucagon. Elevated insulin, low C-peptide, and low proinsulin is consistent with exogenous insulin administration, which would suppress the body’s own insulin production (demonstrated by low C-peptide and proinsulin). Low insulin and insulin precursors can be seen in noninsulin-mediated hypoglycemia: for example, increased metabolic demand from cancers with high tumor burden (such as hepatocellular carcinoma) or tumors secreting insulin-like growth factor (IGF). This diagnosis is unlikely in a patient with no obvious masses on examination and a normal IGF2 level. Our patient demonstrated hypoglycemia (blood glucose <45 mg/dL) coinciding with insulin of 7.9 μIU/mL (2.6 to 24.9 μIU/mL), C-peptide of 2.6 ng/L (1.1 to 4.4 ng/mL), and an elevated proinsulin of 118 pmol/L (3.6 to 22 pmol/L); β-hydroxybutyrate was also low (0.1 mmol/L, normal < 0.4 mmol/L). Given the patient’s hypoglycemia, his “normal” range insulin and C-peptide are inappropriate, as the correct feedback response to a low serum glucose level is a corresponding reduction in insulin production and secretion.

He had a robust increase in glucose level (>25 mg/dL increase), from 55 mg/dL to 96 mg/dL, after 1 mg intravenous administration of glucagon. These findings are consistent with endogenous insulin-induced hypoglycemia secondary to etiologies including insulinoma or noninsulinoma pancreatogenous hypoglycemic syndrome (NIPHS). Given the findings during fasting, our patient underwent imaging to identify any pancreatic tumors. Initial abdominal magnetic resonance imaging (MRI), however, was non-diagnostic, and further endoscopic ultrasound failed to identify any discrete lesion.

4. Given the negative imaging thus far, what would be the next best test?

a) Transabdominal ultrasound
b) Abdominal computed tomography (CT) with contrast material
c) Ga-68 DOTATATE positron emission tomography (PET) scan
d) Selective arterial calcium stimulation test (SACST)
e) Intraoperative ultrasonography

Transabdominal ultrasound and CT are common initial tests in the work-up of suspected insulinoma, as they are quick and noninvasive. However, they are unlikely to reveal new findings, given the negative results of the MRI, which is more sensitive and specific for insulinomas. A DOTATATE PET scan is the appropriate next test. Because neuroendocrine tumors such as insulinomas express high levels of somatostatin receptors, this scan uses a somatostatin analogue to identify insulinoma tumors. A SACST is also an appropriate part of the work-up for insulinoma. However, this is an invasive test, to be performed once noninvasive diagnostic options are exhausted. This test involves injecting calcium gluconate—an insulin secretagogue—into the gastroduodenal, splenic, dorsal pancreatic, and superior mesenteric arteries, respectively, with subsequent measuring of insulin levels from the hepatic vein. A large increase in insulin release (typically 2-fold or greater) after calcium stimulation to a certain pancreatic region suggests the location of hyperfunctional β cells. Intraoperative ultrasonography with palpation of the pancreas is the most sensitive way to detect insulinomas and is performed intraoperatively to resect insulinomas. Because no discrete tumor had been identified thus far, proceeding to surgery would be inappropriate.
After a DOTATATE PET scan failed to identify any pancreatic lesion, the patient underwent SACST. He exhibited increased insulin release with calcium injection into splenic and dorsal pancreatic arteries, consistent with insulin hypersecretion from the pancreatic body and tail. There was no hypersecretion from the pancreatic head with gastroduodenal or superior mesenteric artery stimulation.

5. Given the patient’s refractory hypoglycemia, which one of the following would be the most appropriate treatment?
   a) Dietary modification  
   b) Diazoxide  
   c) Octreotide  
   d) Subtotal pancreatectomy  
   e) Total pancreatectomy

Patients with mild symptoms can often control hypoglycemia by starting a balanced high-protein diet with regularly scheduled meals and snacks. Eliminating foods with high simple carbohydrate content, alcohol, and caffeine, and ensuring that carbohydrates are spaced throughout the day will avoid postprandial insulin spikes and hypoglycemia. This would not be appropriate in our patient with severe symptoms. Diazoxide is a vasodilator with insulin-antagonizing effects. Although it is the first-line pharmacologic treatment for hyperinsulinemia, it does not provide definitive cure and is used when surgery is not an option. Side effects include significant edema, which often necessitates additional medications for management. Octreotide, at high doses, can inhibit insulin; it is a second-line pharmaceutical option because its effects are variable. Surgery provides definitive treatment of hypoglycemia by removing the abnormal \( \beta \) cells. Subtotal pancreatectomy allows the patient to retain the normally functioning portion of the pancreas (pancreatic head) and avoids the need for life-long insulin replacement or complex reconstructive surgery. Total pancreatectomy would be appropriate for a patient with an entirely abnormal pancreas or those who have persistent symptoms following partial pancreatectomy. In this 81-year-old patient, total pancreatectomy would contribute to significant morbidity.

Our patient underwent laparoscopic subtotal pancreatectomy. Pathology revealed a 0.9-cm encapsulated mass in the distal body-pancreatic tail region. Immunohistochemistry stained positive for synaptophysin and chromogranin, suggesting a neuroendocrine tumor. The diagnosis of insulinoma was made.

**DISCUSSION**

Hypoglycemia, in the absence of diabetes or medication, is rare. Symptoms are nonspecific and variable, including palpitations, anxiety, tremor, sweating, paresthesias, fatigue, confusion, behavioral changes, seizures, or loss of consciousness, usually presenting in a repetitive pattern. Work-up of our patient’s “spells” included a thorough history and physical examination to assess for other causes such as benign paroxysmal positional vertigo, orthostasis, cardiac dysrhythmia, seizure, and polypharmacy.

Quantitatively, hypoglycemia is defined as a plasma glucose of <55 mg/dL, as this is when symptoms are expected to develop. However, patients can vary in their threshold for developing symptoms, and therefore we use the Whipple Triad—symptoms of hypoglycemia, low measured plasma glucose level, and symptomatic improvement with raising the plasma glucose level—to better identify patients with hypoglycemic disorders.

In an otherwise healthy-appearing patient, work-up begins by diagnosing hypoglycemia based on laboratory findings and fulfillment of the Whipple Triad. Exogenous or iatrogenic causes of hypoglycemia should be ruled out by screening for hypoglycemia-inducing agents such as sulfonylureas, glinides, or exogenous insulin. In severe cases, alcohol-use disorder can lead to hypoglycemia. Furthermore, in the critically ill hospitalized patient, one may consider severe illness, sepsis, heart disease, kidney disease, or adrenal insufficiency as possible causes of hypoglycemia. In patients who have
undergone Roux-en-Y gastric bypass surgery, postprandial hypoglycemia may be observed. Acquired antibodies to insulin, which irregularly bind and release insulin, is another rare cause of hypoglycemia, most reported in Japanese or Korean patients. Insulinoma or a hyperfunctioning disorder of pancreatic β cells such as NIPHS cause endogenous hyperinsulinemia.8

Although the most common neuroendocrine tumor of the pancreas, insulinomas are overall rare, with an estimated annual incidence of <4 people per million.5,9 In approximately 90% of cases, they are solitary lesions of the pancreas (with even distribution in the head, body, and tail) smaller than 2 cm.5 They are commonly associated with multiple endocrine neoplasia type 1 (MEN-1), occurring in approximately 10% of patients with MEN-1 who often have multiple or more aggressive tumors.4,10 In contrast, NIPHS, sometimes referred to as nesidioblastosis, is not a discrete tumor but rather a β-cell disorder. Although insulinomas are frequently identified during adulthood, NIPHS is more common in infants.10

Differentiating insulinoma from NIPHS involves laboratory testing and imaging. As in our case, some patients may need hospitalization for the duration of work-up given the dangers of refractory hypoglycemia. After screening for hypoglycemia-inducing agents and confirming hypoglycemia is not secondary to another illness, the next step is a supervised fasting screen to confirm endogenous insulin production. A fast of up to 72 hours is sufficient, during which time serial plasma glucose measurements as well as measurements of insulin, C-peptide, proinsulin, and β-hydroxybutyrate are obtained until the patient reaches a blood glucose concentration of 55 mg/dL or less, at which time intravenous glucagon is administered, and the fast is stopped.8 The diagnosis is confirmed if the patient’s hypoglycemia coincides with an inappropriately normal or elevated insulin level above 3.0 μU/mL (2.6 to 24.9 μU/mL), a C-peptide level above 0.6 ng/mL (1.1 to 4.4 ng/mL), an elevated proinsulin level above 5.0 pmol/L (3.6 to 22 pmol/L), and a decreased β-hydroxybutyrate level below 2.7 mmol/L (<0.4 mmol/L). The diagnosis is further confirmed when 1 mg intravenous glucagon results in a plasma glucose increase of more than 25 mg/dL.8 The fast provokes hypoglycemia; however, the diagnosis can be made without this test if laboratory results confirm these criteria during a symptomatic episode.

After laboratory confirmation, imaging should be performed in a stepwise process to try and localize a possible insulinoma. Transabdominal ultrasonography is often used initially; however, it has low sensitivity and specificity for insulinoma.10 Both CT and MRI are appropriate next steps; however, their reported sensitivity and specificity for insulinoma varies widely, ranging from 33% to 64% and 40% to 90%, respectively.5 If no tumor is identified, a DOTATATE PET scan is another noninvasive imaging option, relying on the high affinity of DOTATATE to somatostatin receptors found on neuroendocrine tumors.

Whether or not a tumor is identified thus far, invasive imaging is the next consideration in work-up. Endoscopic ultrasound is often employed, either to identify a tumor if previous imaging is negative or to perform a fine-needle biopsy of a known tumor to confirm diagnosis. This modality is most useful for tumors in the pancreatic head.5 If no tumor is identified, yet the patient’s fasting screen confirms endogenous hyperinsulinism, SACST is performed next. Although SACST cannot always differentiate NIPHS vs insulinoma, it can identify the overactive region of the pancreas to help guide resection. An insulin increase in 2 or more arterial distributions is highly suggestive of NIPHS over insulinoma.11 However, there are cases, such as ours, in which the insulinoma is in a watershed region, receiving more than 1 blood supply, and thus SACST is still positive for 2 different arteries.

Resection of the abnormally functioning pancreas is the appropriate next step. Intraoperative ultrasonography with palpation of the pancreas by an experienced surgeon is the most sensitive test for identifying an insulinoma.5 Surgical pathology confirms diagnosis.
Isolated hypoglycemia, independent of other disease, is rare. Work-up involves confirmation of endogenous hyperinsulinemia (via initial presentation of the Whipple Triad with matching laboratory data or provoking this clinical picture with a fasting study), followed by careful imaging to identify the source of excess insulin secretion. In cases of both solitary insulinoma and NIPHS, surgical resection of the abnormal cells in question can provide curative treatment, with lifestyle modification and pharmacologic therapies offering additional options in patients with mild symptoms or in whom surgery is not feasible.

POTENTIAL COMPETING INTERESTS
The authors report no competing interests.

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CORRECT ANSWERS: 1. e. 2. c. 3. e. 4. c. 5. d.