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Author

Balla, Megana

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CLINICAL VIGNETTE

Primary Adrenal Insufficiency due to Autoimmune Adrenalitis

Megana Ballal, MD

Introduction

Adrenal insufficiency (AI) is a disorder related to inadequate hormone production due to a defect in the hypothalamic-pituitary-adrenal (HPA) axis. Corticotropin-releasing hormone (CRH) is typically secreted from the hypothalamus in response to stress, circadian rhythm and low cortisol. CRH acts on the pituitary gland to stimulate synthesis of adrenocorticotropic hormone (ACTH). This hormone subsequently acts on the adrenal gland, resulting in the release of mineralocorticoids, glucocorticoids and androgens. Adrenal insufficiency is considered primary when the defect is in the adrenal gland, secondary when in the pituitary gland and tertiary when in the hypothalamus. The presentation can be variable, often resulting in a delayed diagnosis. Early recognition and management are crucial in the treatment of AI. Here we describe the case of a young woman diagnosed with primary AI.

Case Report

A 39-year-old woman presented to the emergency department with one week of nausea, vomiting, lightheadedness and fatigue. Her symptoms developed while hiking, which she did on a regular basis. Since that time, she continued to have intermittent symptoms that were worse with minimal activity such as standing and walking. She described a similar presentation seven months ago at which time she was diagnosed with anaphylactic shock secondary to mastocytosis. These symptoms had also occasionally previously occurred aside from that episode, but they were not evaluated as they were less severe and resolved. Her review of systems was remarkable for chronic loose stools but was otherwise negative. Her past medical history included systemic mastocytosis and depression. She took bupropion daily and had discontinued escitalopram one month prior. Past surgical, family and social histories were non-contributory.

In the emergency department, the patient was afebrile with a blood pressure of 87/59 mmHg and a heart rate of 104 beats per minute. She was alert and oriented with a nontender, non-distended abdomen. Initial labs were notable for serum sodium 125 mmol/L, chloride 91 mmol/L, bicarbonate 21 mmol/L. White blood cell count, potassium, creatinine, glucose, lipase and liver enzymes were within normal limits. Given concern for allergic reaction with her history of anaphylaxis, she received intravenous famotidine 20 mg, diphenhydramine 50 mg, dexamethasone 10 mg, ondansetron 4 mg and 1 liter sodium chloride 0.9% and was admitted for hyponatremia. Serum

sodium remained unchanged after intravenous fluids, raising the possibility of hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH) rather than hypovolemia. Stool studies were negative. Additional labs revealed mildly elevated thyroid-stimulating hormone with normal free T4. Urine studies demonstrated sodium 146 mmol/L and osmolality 797 mOsm/kg. Urine culture was negative.

On the second hospital day, she had improved although still reported fatigue and lightheadedness when standing with orthostatic BP changes and serum sodium of 129 mmol/L. Fluid restriction was continued given the suspected diagnosis of SIADH. The following day, the patient reported severe fatigue and dyspnea upon standing. Her nausea and vomiting had resolved. Urine sodium and osmolality remained elevated. Serum sodium increased to 131 mmol/L. Morning cortisol was low at 4 mcg/dL. Subsequent labs demonstrated elevated ACTH at 3002 pg/mL. In consultation with the endocrinology service, an ACTH stimulation test was performed. The patient received 250 mcg of cosyntropin, and serum cortisol was measured after 30 and 60 minutes. The cortisol level did not increase, confirming the diagnosis of primary AI. Upon further questions she reported chronic polydipsia, salt cravings and hyperpigmentation over years.

The patient was discharged on hydrocortisone 10 mg every morning and 5 mg every afternoon as well as fludrocortisone 0.05 mg daily with significant clinical improvement. Thyroid autoantibodies were unrevealing. Plasma renin activity and adrenal antibody resulted positive, after discharge. She was counseled regarding monitoring blood pressure, adjusting the dose of glucocorticoids in the event of illness or stress, and obtaining a medical alert bracelet. She was scheduled for outpatient follow-up to monitor her symptoms and labs including electrolytes and plasma renin activity.

Discussion

Thomas Addison described disease of the suprarenal capsules around the 1850s. His work received subsequent recognition with Armand Trousseau naming the condition Addison's disease.¹ Today this disorder is also known as primary AI. Compared to secondary AI, primary AI is rare with an estimated prevalence of up to 140 cases per million in Western societies.² While prevalence has increased over the decades, this may be partly related to greater awareness of the disease as the

diagnosis can be challenging. Incidence is greater in women with a peak age of diagnosis between 30 and 50 years.³

The presentation of AI can be variable, with nonspecific signs and symptoms especially early on in the disease course. Symptoms can progress over years depending on the degree of mineralocorticoid, glucocorticoid and adrenal androgen deficiency.⁴ Patients can develop fatigue, anorexia, weight loss, nausea, vomiting, postural hypotension, salt cravings and hyperpigmentation. Women can also experience loss of axillary and pubic hair as well as changes in mood due to adrenal androgen deficiency. Hyponatremia is the most common electrolyte abnormality at the time of diagnosis, with other possible laboratory findings including hyperkalemia, hypoglycemia and normocytic anemia.⁵ While our patient was ultimately found to have AI with several characteristic features, the diagnosis was not obvious on initial presentation. Gastroenteritis and SIADH are the most common misdiagnosis in these patients.⁶ A missed diagnosis of AI can lead to a life-threatening emergency known as adrenal crisis. While the exact definition is debated, an adrenal crisis is generally characterized by an acute clinical deterioration often involving hypotension with improvement following administration of parenteral glucocorticoids.⁷ Infection, surgical procedures and other stressors can precipitate this condition.

Further testing is needed to confirm the diagnosis in patients with signs and symptoms suggestive of primary AI. A morning cortisol less than 5 mcg/dL combined with an elevated ACTH level are the typical laboratory findings. Of note, cortisol measurements can be affected by the level of cortisol binding globulin, which increases with estrogen and decreases with liver disease. Plasma renin and aldosterone can also be measured to evaluate for mineralocorticoid deficiency.² An ACTH stimulation test, also known as a cosyntropin test, is generally the next step in diagnosis. After obtaining baseline cortisol and ACTH levels, 250 mcg of cosyntropin is administered and serum cortisol level is measured at 30 and 60 minutes to determine if there is a response to synthetic ACTH. A cortisol level less than 18 mcg/dL is considered diagnostic of primary AI in the setting of an elevated ACTH level.⁴

The next step in evaluation of primary AI is determining the etiology. Autoimmune adrenalitis is the cause in up to 80% of cases in Western countries and can be identified by testing for 21-hydroxylase antibodies. Approximately 50% of patients with this condition develop another autoimmune disorder during their lifetime. Other causes include genetic disease resulting from enzyme defects, malignancy, or infection such as tuberculosis and HIV. Medications can also predispose to this condition. One example is adrenal hemorrhage in the setting of anticoagulation. Other drugs, including antifungals and anti-cancer medications, have also been implicated in the development of primary AI.² In the event of negative antibodies computed tomography can identify adrenal pathology as well as serum very long chain fatty acids to evaluate for adrenoleukodystrophy.⁵

Patients with primary AI require lifelong hormone therapy. Glucocorticoid replacement typically consists of oral hydrocortisone divided into two or three doses for a total of 15 to 25 mg daily. There are no biochemical tests to reliably evaluate for adequate replacement. Therefore, clinicians should monitor parameters such as energy, weight and skin pigmentation to assess for under- or overtreatment.⁵ Prednisone or dexamethasone are considerations for patients who would benefit from once daily dosing. Appropriate sodium and fluid balance is achieved through mineralocorticoid replacement and liberalizing dietary sodium intake. Standard mineralocorticoid therapy consists of fludrocortisone 0.05 to 0.2 mg daily, with monitoring of blood pressure and electrolytes and maintaining plasma renin activity at the upper limit of normal. Women can also benefit from treatment with dehydroepiandrosterone (DHEA) to improve mood, as the adrenal glands are the main source of androgens in this population.⁴ The management of primary AI remains an ongoing topic of research. Novel treatments under investigation include glucocorticoid replacement to better mimic physiologic cortisol secretion as well as immunosuppression for autoimmune adrenalitis, gene therapy and transplantation.²

Patient education is key to preventing adrenal crisis. In general, it is recommended to double the dose of glucocorticoids prior to outpatient procedures or in response to illness or other stressors. An injectable form of glucocorticoid is also advised in the event that the patient is unable to take oral medication. The dose of fludrocortisone may need to be increased in the event of excess salt loss from perspiration. Patients are recommended to carry a steroid emergency card and wear a medical alert identification bracelet to ensure appropriate care is provided in the event of altered consciousness due to adrenal crisis.⁷ Clinicians must be aware of the variable presenting signs and symptoms in order to make a correct diagnosis. In addition, patient education and monitoring are crucial to reduce associated morbidity and mortality.

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