

## CLINICAL QUIZ

# How Much Do You Know About Addison's Disease?

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### WHAT IS ADDISON'S DISEASE?

**A**ddison's disease is characterized by the progressive hypofunction of the adrenal cortex which can affect all age groups.<sup>1</sup>

The adrenal cortex consists of three main layers: the outer zona glomerulosa, the central zona fasciculata and the inner zona reticularis. The zona glomerulosa mainly secretes aldosterone, while the zona fasciculata mainly secretes cortisol. The zona reticularis secretes androgens such as dehydroepiandrosterone (DHEA) and androstenedione, as well as certain glucocorticoids.<sup>1</sup>

Glucocorticoids, such as cortisol, have multiple roles. Cortisol promotes hepatic gluconeogenesis and antagonizes the effects of insulin on glucose metabolism.<sup>5</sup> Glucocorticoids also suppress cell-mediated immunity and have anti-inflammatory properties.<sup>5</sup> Aldosterone mainly regulates extracellular fluid volume by promoting sodium retention and potassium excretion in renal epithelial cells.<sup>5</sup>

Corticotropin-releasing hormone (CRH) from the hypothalamus stimulates the pituitary corticotrophs to release adrenocorticotropin hormone (ACTH), which stimulates cortisol secretion from the adrenal cortex.<sup>5</sup> In the hypothalamic-pituitary-adrenal (HPA) axis, malfunctioning of the adrenal gland is considered primary disease. Any pathology arising from the pituitary and the hypothalamus is considered secondary and tertiary disease, respectively.<sup>5</sup>

The majority of the cases of primary adrenocortical insufficiency in the developed world are caused by autoimmune atrophy of the gland, whereas tuberculosis is a more common cause in developing countries.<sup>3</sup> The less common etiologies include chronic granulomatous infections as well as infiltrative diseases such as amyloidosis, sarcoidosis and hemochromatosis.<sup>3,5</sup> Rare etiologies include HIV infection, adrenoleukodystrophy, adrenomyeloneuropathy, metastatic cancer of various primary origins, bilateral adrenal hemorrhage, familial glucocorticoid resistance and congenital adrenal hypoplasia.<sup>3,5</sup>

Clinical signs and symptoms generally appear after 90% of the adrenal cortex has been functionally destroyed.<sup>5</sup>

The following quiz consists of questions related to Addison's disease. The answers are provided at the end of the quiz.

- 1) The secretion of both glucocorticoids and mineralocorticoids is impaired in Addison's disease.**
  - a) true
  - b) false
- 2) A 28-year old woman presents to a walk-in clinic and believes that she has Addison's disease. If primary adrenal insufficiency is suspected, which of the following features is most likely absent on history and physical examination?**
  - a) orthostatic hypotension
  - b) generalized fatigue
  - c) hirsutism
  - d) weight loss
- 3) In primary adrenal insufficiency, physical examination may reveal increased skin pigmentation in sun-exposed areas, palms, areolae, axillae and mucous membranes. The most widely accepted explanation for the skin changes in Addison's disease is:**
  - a) development of uremic frost that manifests as a muddy complexion in certain areas
  - b) increased production of ACTH, melanocyte-stimulating hormone and beta-lipotrophin that enhance skin pigmentation
  - c) increased iron deposits in the epidermis and mucous membranes manifesting as hyperpigmentation
  - d) enhanced sensitivity to photo-allergic reactions
- 4) Which of the following may precipitate acute adrenal insufficiency in patients with otherwise well-managed Addison's disease?**
  - a) acute infection, septicemia, trauma, surgery

- b) medications such as rifampin, phenytoin, ketoconazole  
c) anti-coagulation therapy  
d) profuse diaphoresis  
e) all of the above
- 5) **A patient in an acute adrenal crisis may have which of the following clinical features?**  
a) neuroglycopenic symptoms: dizziness, seizures, confusion, coma  
b) postural changes in blood pressure and heart rate  
c) severe nausea, vomiting or an acute abdomen  
d) abnormal body temperature (high or low)  
e) all of the above
- 6) **Which of the following is generally not a part of the emergency management of an acute adrenal crisis?**  
a) IV normal saline/5% dextrose  
b) high-dose IV hydrocortisone  
c) ACTH-stimulation testing using cosyntropin  
d) vasopressors in severe crisis as adjuncts to volume repletion
- 7) **Which combination of laboratory findings is most suggestive of Addison's disease?**  
a) hyponatremia, hyperkalemia, hyperglycemia, high ACTH  
b) hyponatremia, elevated renin, low cortisol, low ACTH  
c) hyponatremia, hyperkalemia, low cortisol, high ACTH  
d) hyponatremia, elevated renin, high bicarbonate, low ACTH  
e) 2 of the above
- 8) **A rapid ACTH-stimulation test measures hormone production before and 30 to 60 minutes after an injection of high-dose cosyntropin (synthetic ACTH). Which of the following is false regarding test results 30 to 60 minutes after cosyntropin injection?**  
a) 1° adrenal insufficiency: plasma cortisol remains low or does not rise above normal  
b) 2° adrenal insufficiency: may or may not have significant rise in plasma cortisol in the first hour  
c) 1° adrenal insufficiency: normal plasma aldosterone increment, high plasma ACTH  
d) 2° adrenal insufficiency: normal plasma aldosterone increment, low-normal plasma ACTH
- 9) **A 55-year old male who is an immigrant from South Asia presents to your clinic with features of chronic Addison's disease including hyperpigmentation. Which of the following tests may be most useful in determining the etiology of his clinical findings?**  
a) radioimmunoassay to detect auto-antibodies  
b) chest/abdomen imaging and investigations for bacterial and/or fungal infections  
c) genetic analysis for mutations associated with abnormal functioning of the adrenal cortex and the HPA axis  
d) pituitary imaging for evidence of tumours
- 10) **Addison's disease may co-exist with:**  
a) hypoparathyroidism  
b) chronic mucocutaneous candidiasis  
c) primary hypogonadism  
d) type I diabetes mellitus  
e) all of the above
- 11) **All of the following suggest secondary adrenal insufficiency except?**  
a) history of sudden cessation of prolonged exogenous glucocorticoids  
b) hyperpigmentation is absent  
c) hyperkalemia  
d) triple bolus test fails to adequately increase ACTH secretion
- 12) **Which of following is not a part of the management of adrenal insufficiency?**  
a) advise patient to obtain a Medic Alert bracelet  
b) patients learn to self-inject pre-filled IM dexamethasone to serve as an emergency treatment for a severe stress or trauma, and then contact a physician  
c) prior to a major surgery, high doses of hydrocortisone (e.g. >100mg/d) are accompanied by high doses of fludrocortisone  
d) advise patient to consume adequate sodium  
e) routine follow-up to check for complications of glucocorticoid and mineralocorticoid therapies

## CLINICAL QUIZ ANSWERS

### 1: A

The multiple etiologies of Addison's disease result in the anatomical and/or functional destruction of the three main regions of the adrenal cortex. Clinical signs and symptoms result mainly from glucocorticoid and mineralocorticoid deficiencies.

### 2: C

Loss of androgen secretion results in decreased pubic and axillary hair, which is more apparent in women and more prominent in chronic Addison's disease. In men, hair growth is controlled primarily by androgen production in the testes.<sup>3</sup> Volume depletion, mainly due to lack of aldosterone, causes orthostatic vitals.<sup>3</sup> Lack of cortisol and aldosterone may produce non-specific findings such as weakness (~99% of patients), weight loss (~97% of patients), anorexia and nausea/vomiting (~90% of patients).<sup>5</sup> However, every patient with Addison's disease does not present with all of these symptoms. The diagnosis of adrenal insufficiency in early stages can be difficult due to the subtle clinical presentation.<sup>5</sup>

### 3: B

Loss of negative feedback from cortisol results in enhanced production of ACTH (and its associated peptides, MSH and beta-LPT) from pituitary corticotrophs. A few patients with Addison's disease may paradoxically present with vitiligo, which is associated with an autoimmune etiology.<sup>2,3,4</sup> Hyperpigmentation is not present in 100% of Addison's patients, especially those with an acute adrenal crisis.<sup>3,5</sup> The other statements are either false or not associated with hyperpigmentation in Addison's disease.

### 4: E

Choice a): conditions of physiological stress. Choice b): the medications block steroid production or increase steroid metabolism. Choice c): risk of hemorrhage into the adrenal gland. Choice d): excessive loss of sodium in sweat may cause volume depletion.<sup>3,5</sup>

### 5: E

A patient in an acute adrenal crisis may present with any combination of these findings, or have additional clinical features. Due to the variable presentation of adrenal crisis, prompt recognition requires a high index of suspicion.<sup>1,3,5</sup>

### 6: C

An acutely ill patient should be hemodynamically stabilized. ACTH-stimulation testing is postponed until the patient is stable.<sup>3</sup>

### 7: C

Choice a): patients with Addison's disease are more likely to be hypoglycemic due to the absence of cortisol for gluconeogenesis.<sup>1,5</sup> However, hypoglycemia is rare in adults but a more common presentation in children with Addison's disease.<sup>3</sup> Choice b): an elevated renin may be observed in some patients due to lack of negative feedback by aldosterone. A low ACTH is not found in primary adrenal insufficiency.<sup>5</sup> Choice d): low bicarbonate is generally found due to loss in urine.<sup>1</sup> Mild to moderate hypercalcemia may also occur in 10-20% of patients with Addison's disease, but the exact mechanism is unknown.<sup>5</sup>

### 8: C

Plasma aldosterone levels do not rise upon cosyntropin stimulation in primary adrenal insufficiency.<sup>3,5</sup> Depending on the severity of HPA axis suppression, plasma cortisol levels may or may not rise in the first hour in secondary adrenal insufficiency.<sup>3</sup> If there is a subnormal increase in plasma cortisol with cosyntropin injection, aldosterone and ACTH levels measured from the same blood samples may distinguish between primary and secondary adrenal insufficiency.<sup>5</sup> In primary adrenal insufficiency, plasma aldosterone levels do not rise significantly and ACTH is high. In secondary adrenal insufficiency, plasma aldosterone increment is normal and ACTH is low normal.<sup>5</sup>

### 9: B

A common cause of Addison's disease in the developing world is granulomatous infections caused by bacteria such as *Mycobacterium tuberculosis* and fungi such as *Cryptococcus* and *Histoplasmosis*. Based on the patient's background and clinical findings, the other etiologies are less likely.<sup>3</sup>

**10: E**

Autoimmune Polyglandular Deficiency Syndromes (PDS) consist of multiple endocrine deficiencies and are associated with certain HLA types. Type I PDS generally occurs at an age of 3-5 years and Type II has an adult onset but peaks at ~30 years of age. Type I commonly (but not exclusively) manifests with findings of Addison's disease, chronic mucocutaneous candidiasis, gonadal failure and hypoparathyroidism. Type II commonly (but not exclusively) manifests as Addison's disease, thyroid disease (can be hypo or hyper) and type I diabetes mellitus.<sup>1</sup>

**11: C**

Choice a): Exogenous glucocorticoids (typically if taken longer than 4 weeks) suppress the HPA axis by negative feedback; lack of stimulation with ACTH suppresses glucocorticoid secretion from the adrenal cortex. Most patients recover in a variable period that ranges from days to months. Choice b): Due to low ACTH in secondary adrenal insufficiency, hyperpigmentation is absent.<sup>3</sup> Choice c): The renin-angiotensin-aldosterone system is generally intact in secondary adrenal insufficiency; hyperkalemia is not present due to preserved near-normal aldosterone secretion (which is not inhibited by low ACTH levels).<sup>5</sup> Choice d): A triple bolus test is used in the investigation of pituitary function in patients without any contraindications. The patient is given IV injections of insulin, TRH and LHRH. The insulin

injection induces hypoglycemia which provides a stimulus for ACTH (and GH) secretion. If pituitary function is intact, ACTH levels will rise. In secondary adrenal insufficiency, ACTH levels will not rise.

**12: C**

Very high doses of hydrocortisone (such as >100mg/d) have mineralocorticoid-like effects. Hence, mineralocorticoid replacement with fludrocortisone becomes unnecessary at such high doses of hydrocortisone.<sup>3,5</sup> Although liberal salt intake is generally advised, caution should be exercised to prevent volume overload.<sup>3</sup> The adverse effects of glucocorticoid therapy – of which gastritis tends to be the most common – are rare at the recommended dosages for chronic adrenal insufficiency.<sup>5</sup> The mineralocorticoid therapy is closely monitored in chronic adrenal insufficiency due to the risk of hypertension and hypokalemia.<sup>5</sup>

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