

## Missed Diagnosis of Addison's Disease in Adolescent Presenting with Fatigue.

March 29, 2023

Jimenez S, Crossen S. Missed Diagnosis of Addison's Disease in Adolescent Presenting with Fatigue. PSNet [internet]. 2023.

<https://psnet.ahrq.gov/web-mm/missed-diagnosis-addisons-disease-adolescent-presenting-fatigue>

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### The Case

A 13-year-old girl developed fatigue, weight loss, and a persistent upper respiratory infection over a three-week period. Her parents took her to two hospital emergency departments, two urgent care centers, and her general pediatrician for evaluation; all providers except one of the urgent care centers shared the same electronic health record. Laboratory testing for mononucleosis, group A streptococcus, and anemia was normal. Her leukocyte count was elevated to 18,000/mm<sup>3</sup> with a normal differential. Her basic metabolic panel showed a low serum sodium of 130 mmol/L and a borderline-high serum potassium of 4.9 mmol/L. Two health care providers noted her tanned skin and inquired about use of tanning salons. Her pediatrician noted weight loss and recommended a return visit to recheck her weight, but her parents did not keep the follow-up appointment. She was diagnosed as having either "mono-spot negative mononucleosis" or "culture-negative and ASO-negative strep throat." The family was advised to provide supportive care and counseled that it can take months to recover fully from viral infections.

Over the next several months the patient's symptoms continued. She dropped out of school due to fatigue, sleeping up to 20 hours per day. Shortly after dropping out of school, she developed a new respiratory infection and was taken back to the local emergency department, where she suffered a sudden cardiac arrest. She was successfully resuscitated and airlifted to a tertiary care hospital where the medical team diagnosed her as having an adrenal crisis, later confirmed to be secondary to autoimmune primary adrenal failure or Addison's disease. She was placed on extracorporeal membrane oxygenation to support her cardiorespiratory function but developed massive intracranial hemorrhages and was withdrawn from life support four days later.

### The Commentary

*Commentary by Samantha Jimenez, MD, and Stephanie Crossen, MD*

This is a tragic case of a 13-year-old girl whose death due to complications of adrenal crisis was entirely preventable. She presented to several health care providers with typical symptoms, physical signs, and early laboratory findings suggestive of adrenal insufficiency (AI). Yet the [diagnosis](#) was delayed for several months due to classic [errors in the diagnostic process](#); [premature closure](#) on a more common pediatric diagnosis; [availability bias](#) due to providers' lack of experience with endocrinologic causes of fatigue and weight loss; and [anchoring bias](#) in their failure to consider new diagnostic possibilities despite persistent and worsening symptoms. Unfortunately, this kind of diagnostic delay remains common, with 40-50% of patients experiencing symptoms for over 6 months prior to the diagnosis of AI, and up to 64% undiagnosed until hospitalization.<sup>1</sup>

## Background

The adrenal glands are responsible for producing glucocorticoids, mineralocorticoids, and sex steroids. The inability to adequately produce glucocorticoids or mineralocorticoids can be life-threatening. Adrenal insufficiency (AI) may occur at the level of the adrenal glands (primary), the pituitary gland (secondary) or the hypothalamus (tertiary). As secondary and tertiary AI result from inadequate production of adrenocorticotropic hormone (ACTH), the renin-angiotensin-aldosterone system (primary regulator of mineralocorticoid production) remains able to stimulate the adrenal glands to produce mineralocorticoids. For this reason, secondary and tertiary AI result in only partial adrenal gland dysfunction. In contrast, primary AI affects the production of all three classes of adrenal hormones. Primary AI is rare – affecting on the order of 1 in 10,000 individuals<sup>2-4</sup> – and can be related to autoimmune destruction, infiltration/injury (hemorrhage, trauma, infection), underlying genetic or metabolic disorders, or medication effects. While autoimmune destruction of the adrenal glands (Addison's disease) is the most common cause of adult-onset primary AI, congenital adrenal hyperplasia (CAH) is the most common cause of primary AI among children and is typically diagnosed in infancy.

Common symptoms of AI include anorexia, weight loss, nausea, abdominal discomfort, fatigue, postural dizziness, headaches, and non-specific muscle and joint pain. Patients may also report salt craving if mineralocorticoid production is affected. Skin hyperpigmentation is a unique finding in primary AI due to high levels of ACTH, which is secreted by the pituitary gland to stimulate the malfunctioning adrenal gland, but which indirectly increase dermal melanin production. Skin can appear diffusely tanned – which should raise suspicion if the patient does not report recent sun exposure or artificial tanning – or increased pigmentation can be localized to specific areas such as the mucous membranes, flexural skin surfaces (e.g., knuckles, palmar creases), and areolae. Forms of AI that affect mineralocorticoid production can cause low blood pressure or orthostatic hypotension, and hyponatremia with or without hyperkalemia. Hypoglycemia may also be a presenting sign of AI, although it is more commonly observed in infants and younger children than in adolescents and adults.

Adrenal insufficiency often presents as a slow, progressive illness over many months. This time course and the non-specific nature of AI symptoms make early diagnosis challenging. Many of the symptoms of AI are common presenting symptoms for less serious, self-resolving conditions such as prolonged viral illness. In adolescent girls, symptoms of AI can also be mistaken for an eating disorder.<sup>5</sup> Delay in diagnosis of AI is common – the mean duration of symptoms prior to diagnosis was 5.6 months in one large pediatric cohort<sup>6</sup>

– and can lead to significant morbidity and mortality if the patient suffers an acute adrenal crisis. Adrenal crisis can be precipitated by various forms of physiologic stress including gastrointestinal illness as well as any infection, medical/dental procedure, or physical trauma. Crisis may also occur in patients who are receiving treatment for AI if they miss their daily medications or do not sufficiently increase their steroid replacement doses during physiologic stress. Symptoms of acute adrenal crisis may include vomiting, diarrhea, severe abdominal pain (which can mimic an acute abdomen), fever, neuromuscular weakness, syncope, and confusion. Laboratory findings may include hyponatremia with or without hyperkalemia, metabolic acidosis, hypoglycemia, and hypercalcemia.<sup>5</sup> The patient may present with hypotension or in overt shock, and one in 200 episodes of adrenal crisis is fatal.<sup>7</sup>

### **Approach to Optimize Patient Safety**

This case highlights the challenge of diagnosing a [rare condition](#) with non-specific presenting symptoms, particularly during an isolated patient encounter. Most adolescents presenting with fatigue do not have adrenal insufficiency. However, keeping rare and dangerous conditions (“[zebras](#)”) in the differential diagnosis and avoiding premature closure can optimize patient safety in several ways. In this case, recognizing and documenting AI as a possible cause of the patient’s fatigue could have led to:

1. More explicit communication of this possibility to the family, with clear guidance about what symptoms and time course would be inconsistent with viral illness and should prompt immediate outreach for assistance. The primary care provider in this case appropriately recommended a return visit, which unfortunately was not kept. However, further anticipatory guidance at the time of the initial visit might have prompted the family to seek care differently thereafter.
2. Interpretation of test results (e.g., hyponatremia) and exam findings (e.g., tanned skin) in the context of possible AI, rather than attributing these abnormalities to unrelated factors. In this case, providers commented on the patient’s skin color, but this finding was not felt to be relevant due to the limited differential diagnosis that was considered.
3. Alerting subsequent clinicians who saw her and reviewed her medical notes to consider the diagnosis of AI, particularly given her worsening symptoms. It appears that the initial attribution of her symptoms to a viral illness, and the ready availability of those medical records, led to “anchoring bias” for subsequent providers, who failed to broaden their differential diagnosis.
4. A low threshold for outreach to a subspecialist in endocrinology. Although many communities do not have local access to an endocrinologist, academic medical centers in most states have specialists available for real-time advice via telephone, telemedicine, or e-consultation. Testing and treatment of adrenal insufficiency are complicated and best directed by an endocrinologist (see below), but prompt outreach by the primary provider is critical to ensure this takes place in a safe and timely manner. Outpatient referral to a pediatric subspecialist often takes weeks or months and is not an appropriate first step in cases of possible AI.

Besides including rare and dangerous conditions in the initial [differential diagnosis](#), it is crucial to have a low threshold for re-evaluating the initial diagnosis if symptom progression or severity is not as expected. In this case, the patient’s fatigue lasted several months and progressively worsened, leading to inability to get out of bed. This symptom, in addition to significant weight loss, clearly mandated closer evaluation and

testing. Thorough history-taking and physical examination are necessary at each encounter even if the chief complaint has been addressed by the same or a different provider previously. Although this commentary's primary focus is on AI as a cause of fatigue and weight loss, the differential diagnosis includes chronic infections, autoimmune and inflammatory conditions, malignancies, illicit or prescription drug use, and other endocrine conditions.<sup>8</sup> The initial work-up for chronic fatigue should include, at a minimum, a complete blood count, complete metabolic panel, and thyroid function tests.<sup>8,9</sup> However, additional individualized testing should also be performed – such as testing for pregnancy, autoimmune conditions, systemic inflammation, or specific infections – based on individual exposures and risk factors, physical exam findings, and abnormal blood tests.<sup>8,9</sup>

### **Evaluation and Management of Adrenal Insufficiency**

Evaluation for AI is complicated by the fact that cortisol secretion is both diurnal and pulsatile, so cortisol levels at random times are often low and of little diagnostic value. If a cortisol level is not taken during an expected peak time (7-8 am) or in response to exogenous ACTH administration (ACTH stimulation testing), a low value is not sufficient to diagnose AI. A low cortisol level (<5 ug/dl) paired with an ACTH level greater than two times the upper limit of normal is sufficient to diagnose primary AI, while a cortisol level between 5-14 ug/dl with clinical suspicion for AI should prompt ACTH stimulation testing.<sup>2,10</sup> ACTH stimulation testing is the gold standard evaluation for AI, and involves administering synthetic ACTH intravenously and measuring peak cortisol production at 30 and 60 minutes thereafter.<sup>10,11</sup> A stimulated cortisol level via immunoassay of at least 18 ug/dl indicates an appropriate adrenal response,<sup>10</sup> and more recent studies have shown that a level of 14-15 ug/dl via liquid chromatography–tandem mass spectrometry is also adequate.<sup>12</sup>

Testing for adrenal insufficiency can prove difficult in the acute setting. If adrenal insufficiency is suspected and the patient is not in adrenal crisis at presentation, then targeted testing should be performed under the guidance of an endocrinologist, if available. If the patient is suspected to be in adrenal crisis, they should be treated with high dose steroids immediately to prevent poor clinical outcomes. Ideally serum cortisol and ACTH levels should be obtained prior to steroid administration, but it is NOT necessary to wait for laboratory results before treating with steroids. Confirmatory testing is challenging after a patient has been treated with steroids (which suppress endogenous ACTH and cortisol production), so an endocrinologist should be consulted in these cases to guide adrenal evaluation after steroid administration. In addition, once AI has been diagnosed, an endocrinologist should be involved to determine the etiology and characterize which adrenal hormones are affected, which will impact treatment and prognosis.

Treatment of adrenal crisis should include prompt administration of intravenous or intramuscular hydrocortisone. If a body surface area measurement is available, the patient should be given hydrocortisone 50mg/m<sup>2</sup> (maximum dose 100mg).<sup>8</sup> If height and weight are not available to calculate the body surface area, age-based dosing of hydrocortisone can be given as follows: 25mg for children <3 years old, 50 mg for young children (pre-pubertal) and 100mg for older children/adolescents.<sup>7</sup> Patients should receive aggressive fluid resuscitation with isotonic fluids; hypoglycemia and other electrolyte abnormalities should be corrected; and hemodynamic instability or cardiopulmonary complications should be treated per standard intensive care protocols. High dose intravenous hydrocortisone replacement should be continued for the following 24-48 hours (50-100 mg/m<sup>2</sup>/day, maximum dose 200 mg/day, divided every 6 hours), or

until acute adrenal crisis has resolved.<sup>2,7,10</sup> Thereafter, the patient should be started on maintenance doses of glucocorticoids and mineralocorticoids and educated about appropriate care during illnesses and emergencies by an endocrinology team.<sup>10</sup>

## Take Home Points

- Adrenal insufficiency (AI) is rare among children and adolescents, and often initially misdiagnosed. The most common presenting symptoms of AI are fatigue and weight loss, which worsen progressively over weeks to months.
- Adrenal crisis is life-threatening and can occur in patients with AI due to any physiologic stress, including viral illness or injury. Adrenal crisis must be treated immediately with high-dose steroids to prevent significant morbidity and mortality.
- Including rare and dangerous conditions (“zebras”) in the differential diagnosis for common complaints can prevent premature closure as well as anchoring bias for future providers and may facilitate improved anticipatory guidance to patients/families as well as earlier outreach to specialists for input.
- Diagnostic testing for AI is complicated and best guided by an endocrinologist but measuring serum cortisol and ACTH levels either at 7-8 am or at a time of stress (prior to steroid administration) can be a useful first step in the diagnostic evaluation.

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*This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. [View AHRQ Disclaimers](#)*