Abstract:
A 17-year-old girl with a history of anxiety and emotional dysregulation presented to the emergency department with abdominal pain, weight loss, dizziness, and vomiting. She had previously been prescribed several medications for ongoing somatic and psychiatric complaints, but her symptoms continued to escalate. She was noted to have significant weight loss, orthostatic hypotension, a prolonged QTc on electrocardiogram, and a serum sodium of 130 mEq/L. She was admitted with concern for an eating disorder. While inpatient, her symptoms continued to evolve, and a test was sent that revealed her underlying diagnosis.

Keywords:
chronic abdominal pain; failure to thrive; Addison's disease; primary adrenal insufficiency

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More Than Just Teenage Angst? ☆

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A 17-year-old girl with a history of anxiety and emotional dysregulation presented to the emergency department (ED) with abdominal pain, weight loss, dizziness, and vomiting. She was seen multiple times over the past 4 years for similar symptoms without an organic etiology identified aside from menorrhagia.

She had been referred to the Adolescent Psychiatric Partial Program for anxiety and emotional dysregulation and was found to have significant functional impairment. The partial program identified multiple social stressors which were felt to contribute to her depression and emotional dysregulation, one being the death of her brother 2 years prior. She also experienced issues at school, including social discord and physical altercations. Previously an honor student and the president of her class, she subsequently transferred to a new school, "got mixed in with the wrong crowd," and "started making bad decisions." She also endorsed arguments with her girlfriend, who she had been dating for 2 years. Her academic performance was noted to decline, leading to an academic probation and implementation of tutoring. Following a physical altercation, she was expelled from school. As per the patient, once she was expelled from school, "the stress was so bad that my body started to break down," and "I got sick." She began feeling dizzy, tired, and nauseated all the time. She endorsed anxiety, depression, mood change, trouble sleeping, social isolation, and anhedonia. She also had 2 months of escalating nausea, vomiting, leg pain which interfered with her ability to walk, shortness of breath, "blackouts," and loss of appetite. Additionally, she had occasional lightheadedness, dizziness, chills, and headaches.

The patient had difficulty engaging in the psychiatric partial program secondary to her significant somatic symptoms. She was noted to refuse to join group discussions as she was crying on the floor that she was sick, in pain, and needed to vomit. She did vomit multiple times per day, with higher frequency in the morning, which escalated in the 10 or so days prior to her ED presentation.

In the partial program, she would also sit on the floor frequently, stating that she "could not breathe." She also endorsed significant fatigue, napping for 2-3 hours daily, and was often noted to nap during sessions at the partial program. She reported not eating "because it hurts."

She repeatedly reported no history of active suicidal or homicidal ideation, or psychosis. She denied self-induced vomiting, distorted body image, restrictive eating, binging, or purging; on the contrary, she expressed hope to gain weight. As per her mother, this was "not like her" and she normally "loves food." She denied trauma as well. She stated that she was depressed but denied feelings of hopelessness and worthlessness, and had no suicidal ideation.

Medications included oral contraceptive pills for menorrhagia and dysmenorrhea, as well as alprazolam, citalopram, and ondansetron which were prescribed for her psychiatric and gastrointestinal complaints. She endorsed smoking marijuana to "help me to relax and to help me to eat," which amounted to up to 12 blunts per day, shared with others socially. Family history was significant for diverticulitis and ulcerative colitis.

During her time at the partial program, she was noted to have significant somatic complaints, as well as blood pressures which were "normal but faint and difficult to obtain." On a previous admission to the hospital for these complaints, she was seen by gastroenterology and nutrition consulting services. She was prescribed a proton pump inhibitor, ondansetron and miralax, for dyspepsia and constipation. She noted that her nausea was only relieved by hot showers.

At the time of her presentation to the ED, she had lost 10% of her body weight over the 5 weeks prior to presentation (Figure 1). Furthermore, it was noted that she had an arrest of height growth at less than the fifth percentile at age 13 (Figure 1). She had orthostatic hypotension initially, with heart rate increasing from 88 to 140 and blood pressure decreasing from 83/54 to 75/49 mm Hg on standing. This improved with a normal saline bolus. She was alert, smiling, and cooperative but thin appearing. She also endorsed vague mild tenderness to palpation of her abdomen and thighs. She was noted to have patchy discoloration on her tongue and lips, which she attributed to colored paper that was being used to smoke marijuana.

Results of abdominal and chest radiographs were normal. An electrocardiogram demonstrated a borderline prolonged QTc of 450 (Figure 2). A basic metabolic panel demonstrated a sodium of 130 mEq/L. It also showed an increase in blood urea nitrogen from 17 to 27 mg/dL and creatinine from 0.67 to 0.95 mg/dL over the course of several weeks. Her complete blood count, liver function tests, lipase, and creatine kinase were within normal limits. Her toxicology screen was positive only for cannabinoids, and her pregnancy test was negative.

Because of suspicion of an evolving eating disorder, she was admitted to the medical-psychiatric unit of the hospital for further workup and management of her vomiting, weight loss, and dizziness. During this admission, she had a syncopal event, as well as ongoing vomiting. Her laboratory values worsened, and a test was sent that confirmed her diagnosis.

DIFFERENTIAL DIAGNOSIS

Abdominal pain and emesis in an adolescent are common ED chief complaints with a broad differential. Frequent causes of these symptoms in this population are eating disorders such as anorexia nervosa and bulimia, which often are comorbid with anxiety and/or depression.[1] Our patient had already been given several mental health diagnoses at the time of presentation and was suspected to have an eating disorder on admission. This diagnosis could certainly explain many of her signs and symptoms. Electrolyte imbalances including metabolic alkalosis and hypokalemia can result from self-induced vomiting and diuretic abuse, as well as from aldosterone secretion triggered by volume depletion.[1] Volume depletion may also lead to acute kidney injury, which is reflected in our patient's increased blood urea nitrogen and creatinine. Cardiovascular complications can be seen, including bradycardia, orthostatic hypotension, and a prolonged QTc interval on electrocardiogram; orthostatic hypotension and QTc prolongation were both seen in our patient. The latter is usually due to the previously described electrolyte imbalances or from concurrent QTc-prolonging medications. In our patient, this might be explained by citalopram and ondansetron, both known for QTc prolongation. However, an eating disorder would not explain our patient's significant emesis; she denies self-induced vomiting, and anorexia nervosa alone cannot explain this symptom. Furthermore, she denies a distorted body image and, in fact, hopes to gain weight, sentiments that are inconsistent with an eating disorder. Thus, there is substantial evidence pointing away from an eating disorder as the cause of our patient's symptoms. Although eating disorders are common in the adolescent population, it is important to carefully consider other diagnoses.

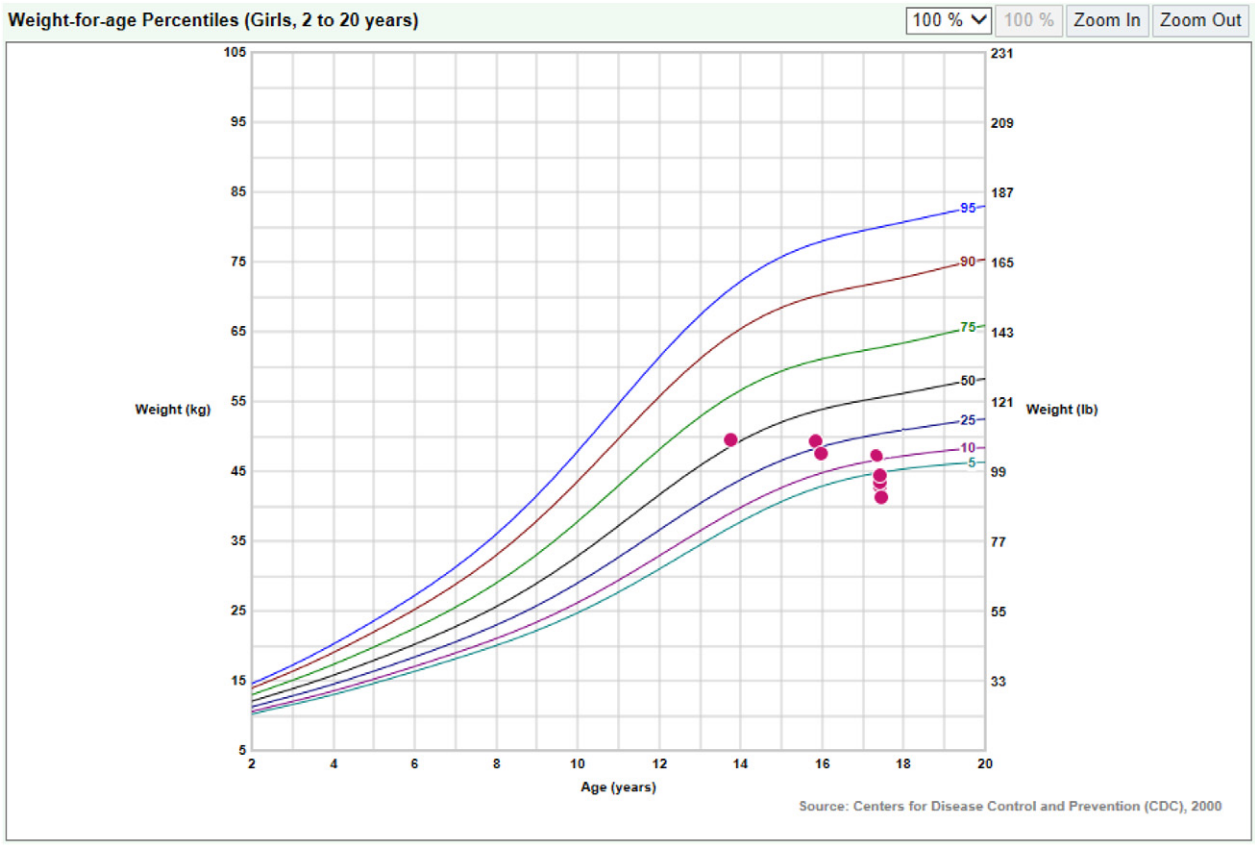

Figure 1 Growth chart at the time of emergency department presentation: (A) weight-for-age percentiles and (B) stature-for-age percentiles.

One possible disorder in the category of functional abdominal pain that may explain some of our patient's symptoms is cyclic vomiting syndrome (CVS), also referred to as *abdominal migraine* because patients often have concomitant migraine symptoms.[2] It is characterized by paroxysms of nausea and vomiting lasting from hours to days interspersed with relatively symptom-free intervals of variable length. The diagnosis is made based on specific clinical criteria, which include having 3 or more

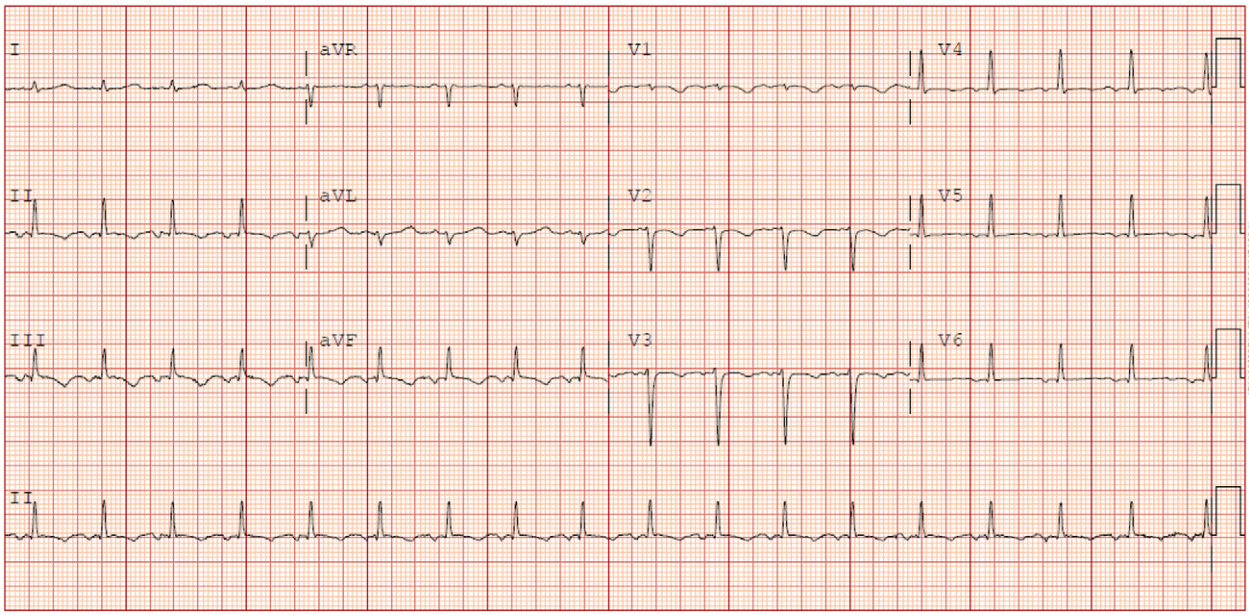

Figure 2 Electrocardiogram demonstrating borderline prolonged QTc of 450, as well as an ectopic atrial rhythm, and diffuse inferolatral T wave flattening/inversion.

stereotypical episodes over the course of the prior year, with onset at least 6 months prior to the diagnosis.[3] Treatment involves avoiding triggers including sleep deprivation, fasting, and physical exhaustion. Psychiatric comorbidities such as anxiety, depression, and autonomic dysfunction may be contributory and should be addressed as well. Prophylactic and abortive therapies such as tricyclic antidepressants, intranasal triptans, and ondansetron may also be considered. This does not seem consistent with what our patient was experiencing, as our patient's symptoms were described as more persistent and escalating, rather than occurring in discrete episodes as in CVS.

This patient endorsed cannabis use; thus, cannabinoid hyperemesis syndrome (CHS), a variant of CVS, must be considered. CHS occurs in chronic cannabis users. It is characterized by intermittent bouts of nausea, vomiting, and epigastric or periumbilical abdominal discomfort which are relieved by hot showers. Symptoms are often predominant in the morning, and patients may experience significant weight loss. Complications include dehydration, acute renal failure, esophageal injuries, and pneumomediastinum.[2] There are several proposed mechanisms as to why CHS occurs. One hypothesis involves downregulation of cannabinoid receptors in chronic use, which abnormally influences the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, in turn causing emesis.[2] Antiemetics like ondansetron and prochlorperazine are frequently ineffective, and patients are more likely to respond to benzodiazepines, haloperidol, and topical capsaicin cream. Given her history of smoking marijuana and a reported positive response to hot showers, this entity may have played a role in her presentation. However, this diagnosis cannot explain the psychiatric symptoms of anxiety and depression that preceded her somatic symptoms, nor can they explain her growth arrest at age 13.

Another possibility is chronic or acute recurrent pancreatitis, both of which most commonly present with abdominal pain, nausea, vomiting, poor growth, and weight loss. The abdominal pain is often characterized as epigastric and radiating to the back, although it may also be described in vague terms. Pediatric pancreatitis has a variety of causes, including structural/congenital anomalies, infections, metabolic derangements, trauma, gallstones, and drugs, among others.[4] Serum amylase and/or lipase is at least 3 times greater than the upper limit of normal. Computerized tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography will demonstrate evidence of pancreatic damage. Management involves pain control, nutrition management, and monitoring for complications. Some children and adolescents develop an intractable disease course characterized by frequent bouts of pain which disrupt their social and academic life,[4] such as was seen in our patient. Such a disease progression could explain our patient's vomiting, pain, growth failure, and weight

loss. However, with a normal lipase, this is unlikely to be the cause of her symptoms.

Acute intermittent porphyria (AIP) is an autosomal dominant disorder of heme biosynthesis which typically presents in women of reproductive age.[5] In this disease, a deficiency of porphobilinogen deaminase leads to an accumulation of aminolevulinic acid and porphobilinogen. The accumulated substrates then act on the central and peripheral nervous systems to produce acute neurovisceral and psychiatric symptoms. Attacks are precipitated by numerous endogenous and exogenous triggers which act on the affected pathway, including certain medications, alcohol, smoking, sex hormones, starvation, and/or stress states. The most common presenting symptom is abdominal pain, as well as vomiting, fatigue, muscle pain, and psychiatric symptoms (ie, irritability, emotional lability, anxiety, and depression), all of which our patient demonstrated. Hyponatremia can also occur in AIP, as seen in our patient, secondary to the syndrome of inappropriate antidiuretic hormone secretion, and/or gastrointestinal or renal sodium loss.[5] Another common component of AIP is peripheral neuropathy, which can involve motor and/or sensory loss, including cranial nerve and respiratory muscle paralysis. Our patient's motor weakness and subjective shortness of breath may have been a manifestation of this, but she did not experience any sensory or bulbar symptoms. It also often involves autonomic manifestations like tachycardia and hypertension. In contrast, our patient demonstrated orthostatic hypotension. Furthermore, AIP frequently causes dark or reddish-brown urine secondary to an accumulation of porphyrins and/or porphobilin in the urine, which our patient did not have. Diagnosis involves the detection of increased porphobilinogen in the urine or plasma, and treatment requires trigger avoidance and glucose and hemin therapy.

Lastly, celiac disease (CD), also known as *gluten-sensitive enteropathy*, an autoimmune disease of the small intestine caused by a sensitivity to dietary gluten, may be responsible for our patient's symptoms. Although "classic" CD presents with abdominal pain and chronic diarrhea, it may also present with vomiting in the absence of diarrhea.[6] This entity often has nonspecific associated symptoms and could explain our patient's anorexia, weight loss, fatigue, and height growth arrest. Depressive symptoms and disruptive behavioral disorders, as experienced by our patient, are also highly common in adolescents with CD.[7] Diagnosis requires serologic testing for tissue transglutaminase immunoglobulin (Ig)A antibody. IgA levels must be tested as well because concomitant IgA deficiency can cause a falsely negative tTg-IgA result. If these serologies are consistent with CD or if suspicion persists despite a negative level, the diagnosis is established through an endoscopy with biopsy. Treatment is strict adherence to a gluten-free diet.

CASE PROGRESSION AND DIAGNOSIS

During her admission, the patient was noted to have a bronzed appearance, without tan lines, in addition to her previously noted discolored lips. She also had worsening hyponatremia to 127 and hyperkalemia to 5.9. The team was concerned for adrenal insufficiency based on these findings. They consulted the pediatric endocrinology service and sent adrenocorticotropic hormone (ACTH) and cortisol levels. While these values were still pending, the patient was started on stress dose steroids, with substantial improvement in her symptoms. Her ACTH ultimately resulted as elevated at 3156 pg/mL (normal 9-57), and her cortisol was low at 1.3 μg/dL (normal 3.0-16.0). These findings led to the diagnosis of Addison's disease.

ADDISON'S DISEASE

Addison's disease, also known as *primary adrenal insufficiency*, is the impaired synthesis and release of adrenocortical hormones. Unlike secondary adrenal insufficiency which results from impaired central production of ACTH, primary adrenal insufficiency results from disease intrinsic to the adrenal gland. For children in the developed world, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia followed by autoimmune adrenal insufficiency.[8] Worldwide, however, the second most common cause is glandular infiltration by tuberculosis.[8,9]

The manifestations of Addison's disease are mainly a result of glucocorticoid (ie, cortisol) and mineralocorticoids (ie, aldosterone) deficiencies. Cortisol stimulates gluconeogenesis and catabolizes protein and fat, thus increasing glucose and providing substrates for essential tissues such as the brain and red blood cells during times of stress and starvation.[8] It also helps to maintain blood pressure through sodium and water retention, as well as through a permissive effect on catecholamines.[8,9] Aldosterone is responsible for stimulating the reabsorption of sodium and secretion of potassium and hydrogen ions in the kidney.

The deficiency of these important hormones results in nonspecific symptoms including anorexia, fatigue, nausea, vomiting, weakness, hypoglycemia,

orthostatic hypotension, behavior changes and depression. It can also result in dehydration, weight loss, hypoglycemia, hyperkalemia, hyponatremia, volume depletion, and a metabolic acidosis. Rarely, hypercalcemia may be seen secondary to decreased renal excretion of calcium and bone resorption. The most distinguishing physical characteristic seen in this disorder is hyperpigmentation, particularly in the skin creases and buccal mucosa. This occurs from increased production of proopiomelanocortin, a precursor to ACTH, melanocyte-stimulating hormone, and others.[8] The increased melanocyte-stimulating hormone results in promotion of melanin synthesis, which in turn causes hyperpigmentation. These symptoms are quite nonspecific, appear insidiously, and can easily be misdiagnosed as a gastrointestinal illness or eating disorder, as was the case in our patient. Importantly, electrolyte disturbances can be quite helpful in prompting the diagnosis, but they may not appear until later in the course. In particular, hyponatremia may occur prior to hyperkalemia and may thus be erroneously attributed to alternative causes of fluid depletion. Androgen depletion is another consequence of Addison's disease and may manifest in women as low libido, depressive symptoms, and decreased axillary and pubic hair.

Adrenal crisis often presents with severe weakness, abdominal pain, nausea, vomiting, and altered mental status. The patient often is hypotensive and febrile, with abdominal tenderness and possible guarding. This may easily be mistaken for an acute abdominal process. Thus, the physician must have a high index of suspicion for adrenal crisis and look for concurrent electrolyte abnormalities including hypoglycemia, hyponatremia, hyperkalemia, and hypercalcemia.

The most important aspects in treating adrenal crisis are fluid resuscitation and steroid replacement. Isotonic sodium chloride 0.9% should be used to correct hypovolemia and hyponatremia. The patient should receive 20 mL/kg rapidly, which can be repeated up to 60 mL/kg within the first hour, followed by a continuous infusion guided by the patient's individual needs. If sodium is corrected too rapidly, the patient is at risk for osmotic demyelination syndrome. Stress dose hydrocortisone, which has both glucocorticoid and mineralocorticoid activity, should be given empirically and can be administered intramuscularly or intravenously. The dosing may be based upon body surface area (50 to 100 mg/m^2), but for more rapid treatment, the following age-based dosing can also be used: 25 mg for infants, 50 mg for school-age children, 100 mg for adolescents.[10] Hypoglycemia should be corrected with intravenous dextrose at 2-4 mL/kg of D25W to a maximum single dose of 25 g infused slowly at a rate of 2 to 3 mL/min, or 5-10 mL/kg of D10W for children younger than 12 years old.

In unstable patients in whom the diagnosis of adrenal insufficiency is suspected but not yet confirmed, empiric treatment should be started immediately without awaiting diagnostic testing. Serum levels of cortisol, ACTH, aldosterone, dehydroepiandrosterone sulfate, and renin can be useful in diagnosis and should be drawn just prior to hydrocortisone administration, if possible. A low cortisol level in the early morning or in a state of stress supports the diagnosis, as does an elevated ACTH level, for primary adrenal insufficiency. The criterion standard for diagnosis is the corticotropin or ACTH stimulation test, which should be performed after the patient has been stabilized.

The treatment for Addison's disease is glucocorticoid and mineralocorticoid replacement therapy, as well as dehydroepiandrosterone replacement in symptomatic women. Glucocorticoids should be replaced with hydrocortisone at a total starting daily dose of 8 mg/m^2 body surface area and adjusted toward individual needs.[10] Those with confirmed aldosterone deficiency should receive replacement with fludrocortisone at a starting dose of 100 μg/d.[10] Parents and children should be educated about glucocorticoid adjustments in times of stress, including self-administration of parenteral stress-dose steroids. They should also carry a steroid emergency card and a medical alert band so that emergency clinicians can act to prevent or treat an adrenal crisis in case of an emergency.

SUMMARY

Here, we present a case of a 17-year-old girl with multiple previously diagnosed conditions including anxiety, reflux, somatic symptom disorder, chronic abdominal pain, cannabinoid hyperemesis syndrome, and dysmenorrhea who was ultimately diagnosed with primary adrenal insufficiency or Addison's disease. At any point in her course, it would have been easy to fall prey to anchor bias and to attribute her symptoms to any of the prior diagnoses that had been made. However, emergency medical clinicians must remember to think critically about each new patient despite what prior diagnoses they may carry. In particular, primary adrenal insufficiency can develop quite insidiously, making diagnosis difficult. It should be considered in patients with nonspecific complaints of fatigue, nausea, vomiting, abdominal pain, and diarrhea in the ED and in those presenting with psychiatric

symptoms, particularly depression. Furthermore, the metabolic derangements may be slow to develop, and the patient may demonstrate hyponatremia prior to the onset of hyperkalemia. Thus, the absence of these specific abnormalities cannot rule out the condition. Lastly, if high clinical suspicion exists for adrenal insufficiency, the provider should consider stress-dose steroids while awaiting definitive test results. ✚

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