You are seeing a 14-year-old white male athlete with atopy who complains of a 6-month history of progressive proximal muscle weakness, which significantly impacts his ability to run short distances and swing his baseball bat. His mother states he has presented to multiple emergency departments (ED) for continued weakness and that most diagnosed him with dehydration and educated the family on how to maintain fluid balance.

At his last ED visit, a creatine kinase (CK) level was drawn and found to be elevated at 1,247 U/L (normal range 9-185 U/L). A referral to a neurologist was made. The neurologist noted worsening fatigue, dizziness, and a documented 17-pound weight loss at the patient’s initial visit. A possible infectious versus progressive inflammatory myositis was suspected. The neurologist recommended an electromyography (EMG) to evaluate the patient’s proximal muscle weakness.

Prior to completion of this EMG, the teen presents to your clinic now complaining of pre-syncopal events. On further review of symptoms, you note the patient has persistent polydipsia, headaches, nausea/vomiting, intermittent abdominal pain, and hyperpigmentation. Family history is negative for myopathies or dystrophies, but positive for hypothyroidism (mother), pineal gland tumor (father), and rheumatoid arthritis (maternal grandmother).

PHYSICAL EXAMINATION

Initial physical examination reveals an afebrile, thin, adolescent male with orthostatic blood pressure changes of 113/59 mm Hg at rest and 89/44 mm Hg while standing; a pulse of 87 beats/min; and a respiratory rate of 16 breaths/min. His HEENT exam reveals equally reactive pupils with moist mucous membranes and no thyromegaly. His neurologic exam including cranial nerves, mental status, speech, gait, and coordination is unremarkable; there is no tremor noted.

His muscle strength is noted to be 4/5 in the quadriceps bilaterally but 5/5 throughout the rest of his muscle groups. His muscle bulk and tone are mildly decreased. His cardiovascular, pulmonary, and abdominal exams are all benign. He has physiologic pubertal gynecomastia with mild tenderness. His genitourinary examination reveals normal appearing Tanner 3 male genitalia. His skin exam is remarkable for diffuse hyperpigmentation, which extends into his intertriginous areas and most notably the palms and creases of his hands. Flexor surfaces on his arms and diffuse areas on his face show ec-
ematous plaques. In comparison to his first-degree family members, he was noticeably darker (see Figure 1; Figure 2, page 205; and Figure 3, page 206).

QUESTIONS
Based on the patient’s history, physical examination, and abnormal laboratory results, which initial common test should you perform?

Does this patient warrant further evaluation in a hospital setting or can he be safely discharged home? What is your differential diagnosis?

CASE DISCUSSION
Given the progressive weakness, presyncope with demonstrated orthostatic blood pressure changes, and hyperpigmentation, you decide to transport the patient to the nearest ED for lab work, fluid resuscitation, and further evaluation. You suspect an underlying endocrine disorder, given that the skin changes and symptoms are often associated with a pathological adrenal process. You ask the ED attending to send stat serum electrolytes. In addition, you request blood urea nitrogen, creatinine, liver function tests, creatine kinase, a urinalysis, and a complete blood count with a differential. Your patient is then admitted to the inpatient service on maintenance fluids.

Whereas most of his results return within normal limits, his serum sodium level is low at 122 mEq/L (normal 134-149 mEq/L), his white cell differential reveals 11% eosinophils (normal 1% to 3%) and his CK remains elevated at 567 U/L. Concern for infection is reduced with a normal white count and rhabdomyolysis is ruled out with a CK < 1,000 U/L and an unremarkable urinalysis when blood or myoglobin is not detected.

Further investigation leads to the discovery of a markedly elevated ACTH at 2,155 pg/mL (normal < 52 pg/mL), low aldosterone levels (< 4 ng/dL), high plasma renin activity (32 ng/mL/h), and positive 21-hydroxylase antibodies (normal negative titer). Autoimmune adrenal insufficiency, also known as Addison’s disease (AD), is confirmed. Your patient is started on stress doses of hydrocortisone for 2 days then begins 10 mg every morning with 5 mg every afternoon and evening and fludrocortisone 0.1 mg daily. Further exploration into his disease process is initiated. His symptoms and most of his laboratory abnormalities quickly resolve with replacement of his hormonal deficiencies.

Prior to discharge, additional basic endocrine labs that reveal additional concerns are sent. The patient has an elevated thyroid-stimulating hormone (TSH) of 7 mcU/mL (normal, 0.30 mcU/mL to 4.00 mcU/mL) with normal free T4 of 1.1 ng/dL (normal, 0.9 ng/dL to 1.7 ng/dL). He also has positive thyroid peroxidase antibody titers of 5,120 (normal negative titer) and a thyroglobulin antibody titer of 160 (normal negative titer).
titer), leading to an additional diagnosis of Hashimoto’s thyroiditis (HT). At this point, you now have a patient with multiple endocrinopathies consistent with a diagnosis of autoimmune polyendocrine syndrome and, thus, require further instruction on how to manage him.

An interesting aspect of this case is the abnormal elevation of your patient’s CK that you noticed during his initial presentation. This lab result is quite atypical for patients with AD alone. Elevation of CK > 1,000 U/L is diagnostic criteria for rhabdomyolysis and can be associated with a multitude of medical conditions.1

Literature suggests that hyponatremia could have been a causative mechanism for muscle damage leading to the patient’s elevated CK level. Multiple recent case studies have documented this phenomenon.2-4 They suggest that fluctuations in the intra- and extra-cellular osmolality in the face of a patient with significant hyponatremia and muscle fatigue could have led to cellular edema, extrusion of intracellular potassium, and disruption of the cellular membrane resulting with release of CK from apoptotic myocytes.5-8 Given the elevated CK along with his AD, it is safe to conclude your patient had hyponatremic rhabdomyolysis, which should resolve over time.

AUTOIMMUNE POLYENDOCRINE SYNDROMES

There are four different types of autoimmune polyendocrine syndrome (APS), types I to IV. Their presentation and manifestations are quite varied, and therefore careful attention to clinical and laboratory evaluation is important (see Table 1). The term “polyendocrine” itself may be a misnomer because some patients have multiple endocrine disorders while some have many nonendocrine issues.9 Prompt recognition of APS is crucial because it may require that a patient or family member undergo further evaluation for certain genetic syndromes or autoimmune disorders.

APS type I often appears early in life, typically in infants with chronic candidal infections, hypoparathyroidism and autoimmune AD.10 This syndrome is rare, but appears with increased prevalence in certain populations and has a familial component with a known autoimmune regulator (AIRE) gene mutation as a cause of the syndrome.9 Patients with any two of either mucocutaneous candidiasis, hypoparathyroidism, and AD almost always have an AIRE mutation.5 The AIRE gene is an autosomal recessive gene that is responsible for intrathymic presentation of a number of autologous antigens. Mutations in AIRE genes cause several combinations of autoimmune endocrine diseases most likely because the appropriate self-antigens are not properly presented in the thymus.11

APS type II (also called Schmidt’s syndrome with AD plus type 1 diabetes mellitus [T1DM] or HT), though rare, is much more common and more varied in its manifestations than APS type I.12 The patient discussed in this article was eventually diagnosed with APS II (see Table 2, page 206). The incidence of APS II is 1.4-2.0 per 100,000 inhabitants.12 Associations include hyperpigmentation and vitiligo as well as a several-year history of intermittent, severe hypoglycemia and intermittent, severe fatigue.10

Simultaneous diagnosis of primary adrenal insufficiency and thyroid disease or T1DM (or both) does not necessarily confirm a diagnosis of APS II. An autoimmune basis for the components of the syndrome must be demonstrated to confirm the diagnosis. The presence of 21-hydroxylase autoantibodies is highly sensitive and specific for primary adrenal insufficiency of autoimmune origin.13 Thyroid peroxidase autoantibodies (80% to 90% of patients) and thyroglobulin autoantibodies (60% to 70% of patients) are detected in patients with HT.14 Islet cell antibodies can be demonstrated in about 80% of patients with new-onset T1DM.15 Glutamic acid decarboxylase 65 autoantibody is the marker with the highest diagnostic sensitivity for T1DM.14 AD is present in 100% of cases, HT or other autoimmune thyroid diseases in 69% to 82% and T1DM in 30% to 52% of patients.10

### Table 1. Classification of APS

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Chronic candidiasis, chronic hypoparathyroidism, autoimmune AD (at least 2 present)</td>
</tr>
<tr>
<td>II</td>
<td>Autoimmune AD + autoimmune thyroid diseases and/or type 1 DM (AD must always be present)</td>
</tr>
<tr>
<td>III</td>
<td>Thyroid autoimmune + other autoimmune diseases (excluding autoimmune AD)</td>
</tr>
<tr>
<td>IV</td>
<td>≥ 2 autoimmune diseases (that do not fall in types I, II, or III)</td>
</tr>
</tbody>
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AD = Addison’s disease; APS = autoimmune polyendocrine syndrome; DM = diabetes mellitus.

Adapted from Neufeld and Blizzard17

Figure 2. Hyperpigmentation of the palmar surface of the patient’s hand.
About half of patients with APS II, including our patient, have relatives with autoimmune disorders.\(^16\)

APS type III refers to thyroid autoimmunity plus another autoimmunity (excluding autoimmune AD) and APS type IV refers to two or more other organ-specific autoimmune diseases.\(^17\) Some literature refers to APS I-IV as separate entities, yet some clump types II-IV as type II.

Autoimmunity precedes overt AD by years. AD — either as part of APS type or as an isolated condition — is a complex genetic disorder with a specific HLA-DR and HLA-DQ genotype that confers high risk.\(^8\) Because up to 50% of patients with autoimmune adrenal insufficiency may develop APS II, adults with the condition should be screened for thyroid disease and diabetes every 5 years.\(^18\) However, only 1% of patients with thyroid disease will develop adrenal insufficiency; therefore, routine screening for other autoimmune diseases is not cost-effective in patients with just thyroid disease.\(^16\)

In patients at risk for APS who have a single disorder such as AD or T1DM, the prevalence of other autoimmune diseases is 30 to 50 times higher than the general population.\(^19\) This is an important point to remember when considering comorbid disease processes that may present months to years later.

**DIAGNOSIS OF APS**

It is important for clinicians to know when and what to screen for in patients with APS and to educate patients about other potential symptoms. These include symptoms of AD (hyperpigmentation, fatigue), T1DM (polyuria, polydipsia and polyphagia), pernicious anemia (problems with coordination), hypothyroidism (fatigue, weight gain, hair changes), and celiac disease (abdominal pain, anemia) among others.

When a disease is suspected, the evaluation should be no different, even if multiple endocrine abnormalities or symptoms are present. For example, for patients in which AD is presumed, diagnostic testing remains the same. Physicians can send a morning cortisol level, usually between 6 a.m. and 8 a.m. when levels should be at their highest, to rule out adrenal insufficiency.\(^20\) Levels less than 3 mcg per dL are suspicious for adrenal insufficiency.\(^21\) However, the diagnostic gold standard for AD is the cosyntropin stimulation test (synthetic adrenocorticotropic hormone [ACTH]) and yields both high sensitivity and specificity.\(^22\)

During this test, a 250-mcg intramuscular or intravenous ampule of cosyntropin is given at any time in the day and the level of cortisol is measured within 1 hour after administration.\(^21,23\) If a patient has primary adrenal insufficiency, the cortisol level will not respond to stimulation (normal response greater than 18 mcg/dL) and will remain low, and the baseline ACTH level is high.\(^21\)

Additional studies suggest setting a lower level of 14 mcg/dL to avoid false positive results and to increase screening sensitivity.\(^24\) This patient did not have a stimulation test and instead demonstrated low morning cortisol levels with a markedly elevated ACTH level (also diagnostic for AD).
Diagnostic testing for the other diseases associated with APS is simpler. For example, hypothyroidism is diagnosed with low serum-free T4 levels and elevated levels of thyrotropin secreting hormone. T1DM is confirmed by elevated fasting serum glucose levels or elevated HbA1c, and the recommended diagnostic screen for celiac disease is the presence of anti-tissue transglutaminase (anti-tTG) immunoglobulin A (IgA) and/or IgA endomysial antibodies, with normal IgA levels.

Yet, an important distinction between a patient with multiple unassociated endocrine abnormalities and a patient with APS is the presence of auto-antibodies. As discussed earlier, these antibodies play a prominent role in the development of these patients’ disease processes and should be tested whenever a diagnosis of APS is considered.

**TREATMENT OF APS**

The treatment of APS focuses on which particular manifestation or symptom is taking place at the time of presentation and should be done in consultation with a pediatric endocrinologist. For example, patients with symptomatic adrenal insufficiency often undergo replacement therapy with hydrocortisone. Much like our patient, higher doses of hydrocortisone are usually required in the morning, but additional lower doses after lunch or in the evening are needed. Initial doses of hydrocortisone are typically given at stress levels, then maintenance is provided usually range between 20 mg and 25 mg divided throughout the day (example, 15 mg in the morning, 10 mg at night) or 10 to 25 mg/m²/day to 12 mg/m²/day (some literature state as low as 6 mg/m²/day to 8 mg/m²/day is adequate), and is dependent on the degree of cortisol deficiency.

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This approach aims to prevent common side effects associated with chronic steroid use such as osteoporosis, hypertension, and increased adiposity.

Due to persistent aldosterone deficiency for patients with APS who also have AD, supplementation with fludrocortisone is needed. These doses usually range from 0.05 mg to 0.2 mg daily and are often dependent on control of the patient’s serum electrolytes, plasma renin activity, and blood pressure.

If this does not occur and persistent elevation of thyrotropin levels remain, titration of levothyroxine should be based on degree of thyroid dysfunction as noted with changes in laboratory values over time. Other components of autoimmunity must be treated according to their typical therapies.

**CONCLUSION**

All forms of APS are much more common in adults, women, and people who have the predisposition for autoimmunity. The patient in this case did not fit any of these characteristics; he presented with a myositis with an elevated CK, a presentation that led him to be initially evaluated by neurology rather than endocrinology. It is likely both of his underlying deficiencies played a role in the eventual discovery of APS.

Since discharge and with your continued management as their primary care physician, the patient’s symptoms have improved tremendously on replacement corticosteroid and mineralocorticoid. Due to the nature of his illness, you have screened for type 1 diabetes, pernicious anemia, celiac disease, and autoimmune hypogonadism, with all results negative at this point. However, you continue to screen for symptomatology at each follow-up visit. His electrolytes have since corrected and are within normal limits. He has returned to athletics and is no longer struggling to keep up with his peers.

**REFERENCES**


All patients with adrenal insufficiency are advised to wear warning bands and carry information regarding their medical regimen.

All patients with AD must be educated on the importance of stress-dose steroid replacement during acute febrile illness, episodes of continued vomiting, or during illness in which weakness or fatigue is a predominating constitutional symptom. This is usually accomplished by tripling their daily hydrocortisone dose. Additionally, all patients with adrenal insufficiency are advised to wear warning bands and carry information regarding their medical regimen with them at all times in case of an emergency.

It is crucial to remember that in patients with AD and HT, thyroid replacement should be initiated after gluco- and mineralo-corticoid replacement, since initial thyroid replacement can precipitate an adrenal crisis. This occurs secondary to the action of T4 in increasing hepatic corticosteroid metabolism. Furthermore, in some patients with AD with thyroid autoantibodies and thyrotropin levels below 30 mcU/mL, thyrotropin levels may normalize after glucocorticoid replacement.

**FEATURE**

All patients with celiac disease are advised to avoid gluten in their diet. It is important to note that the diagnosis of celiac disease is often missed as they present with gastrointestinal symptoms alone.

**FEATURE**

All patients with type 1 diabetes are encouraged to carry information regarding their medical regimen and to wear warning bands.