Autoimmune Polyglandular Syndrome, Type II

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The combination of autoimmune adrenal insufficiency with autoimmune thyroid disease and/or type 1 autoimmune diabetes mellitus defines autoimmune polyglandular syndrome, type II. The conditions may occur in any order, and diagnosis is confounded by the nonspecific nature of the symptoms of adrenal insufficiency and hypothyroidism. The disorder is not common, but consequences can be life threatening when the diagnosis is overlooked. The conditions usually present in midlife, and women are affected more often than men. The cosyntropin test is recommended for diagnosing adrenal insufficiency, which must be present to diagnose this syndrome. Hormone therapy for each condition is similar to treatment that would be provided if the conditions occurred separately, except that treatment for adrenal insufficiency must be given before thyroid therapy is started when the conditions occur together. (Am Fam Physician 2007;75:667-70. Copyright © 2007 American Academy of Family Physicians.)

Autoimmune polyglandular syndrome, type II (APS II) is not a common disease, but it has life-threatening consequences when the diagnosis is overlooked. APS II is the combination of chronic autoimmune adrenal insufficiency (i.e., Addison's disease) with autoimmune thyroid disease, type 1 autoimmune diabetes mellitus, or both. Other associated conditions are listed in *Table 1*.[1]

Epidemiology

The incidence of primary adrenal insufficiency is estimated at about five cases per 100,000 persons in the United States.[2] In Europe, the occurrence of the disease is increasing[3] and is estimated at 11 to 14 per 100,000 persons.[4] Before the advent of effective chemotherapy, tuberculosis was the most common cause worldwide, but current reports indicate that autoimmune disease accounts for 44 to 94 percent of primary adrenal insufficiency.[5]

It has been estimated that as many as one fourth of patients with one autoimmune disease will develop another one during their lives.[6] This happens in about 50 percent of patients with autoimmune adrenal insufficiency.[2] The prevalence of APS II has been estimated at 1.4 to 2.0 per 100,000.[1] It can occur at any age but most commonly occurs in patients 30 to 40 years of age. Women are affected three times more often than men.[7] In about 50 percent of cases of APS II, adrenocortical insufficiency is the initial endocrine abnormality.[7]

Genetics

Approximately one half of patients with APS II have relatives with autoimmune disorders.[8] As with most autoimmune disorders, the predominant known genetic determinant of susceptibility to APS II resides in the human leukocyte antigens (HLA) region (i.e., major histocompatibility complex). The class II HLA haplotypes DR3 (DQB*0201) and DR4 (DQB1*0302) are strongly linked with component disorders of this syndrome. It is highly likely that there is a complex interaction between non-HLA loci and environmental factors.[9]

Clinical Presentation

Symptoms of adrenal insufficiency are nonspecific and common to many other conditions, and they may fluctuate in the early stages of the disease. Common signs and symptoms are listed in *Table 2*. Fatigue may be occasional or may progress to profound, chronic fatigue requiring bed rest. Associated changes such as darkening of the skin, which is especially noted in skin creases or in the oral mucosa, and patches of vitiligo (i.e., loss of pigmentation) also may occur.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Adrenal insufficiency should be diagnosed using the cosyntropin (Cortrosyn) test.	C	11, 13
Each condition of autoimmune polyglandular syndrome should be treated the same way they would be if they occurred separately.	C	1, 7, 17, 18

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 603 or http://www.aafp.org/afpsort.xml.

Fair-skinned patients may appear to have a suntan that does not fade. Hypotension, hypoglycemia, and hyponatremia are fairly late manifestations. Ovarian failure occurs in 10 percent of women with APS II,[7] so amenorrhea in a woman younger than 40 years may warrant consideration of this diagnosis. Alopecia occurs in 1 to 4 percent of patients with APS II.[7] Conversely, up to 15 percent of patients with alopecia (areata, totalis, or universalis) have autoimmune thyroid disease.[7] Ideally, physicians would identify patients with APS II before symptoms become severe, to avoid potential morbidity and mortality of the syndrome.

TABLE 1
Conditions Associated with Autoimmune Polyglandular Syndrome, Type II

Conditions	*Percent of patients affected*
Required for diagnosis	
Autoimmune adrenal insufficiency	100
Autoimmune thyroid disease	69 to 82
Type 1 autoimmune diabetes mellitus	30 to 52
Other associated conditions	
Vitiligo	4.5 to 11.0
Chronic atrophic gastritis, with or without pernicious anemia	4.5 to 11.0
Hypergonadotropic hypogonadism	4 to 9
Chronic autoimmune hepatitis	4
Alopecia	1 to 4
Hypophysitis	< 1
Myasthenia gravis	< 1
Rheumatoid arthritis	< 1
Sjögren's syndrome	< 1
Thrombocytic purpura	< 1

Information from reference 1.

Diagnostic Testing

In the absence of corticosteroid-binding globulin deficiency, an unstimulated serum cortisol sample drawn between 6:00 and 8:00 a.m. may be useful, because a level less than 3 mcg per dL (80 nmol per L) strongly suggests adrenal insufficiency, and levels of 8 mcg per dL (221 nmol per L) or greater exclude the diagnosis of adrenal insufficiency.[10] In acutely ill patients, basal cortisol levels vary greatly and may not be useful.

The standard test for primary adrenal insufficiency is the cosyntropin (Cortrosyn) test (synthetic adrenocorticotropic hormone [ACTH]), which has 95 percent sensitivity and 97 percent specificity.[11] One ampule (250 mcg) of cosyntropin is given intramuscularly or intravenously, and the plasma or serum cortisol level is measured 30 to 60 minutes later.[12] In a normal (negative) test result, the serum cortisol level is usually greater than 14 mcg per dL (390 nmol per L). A serum cortisol level less than 14 mcg per dL is considered positive and indicates an increased probability of primary or secondary adrenal insufficiency. The test can be done at any time of day. A basal cortisol level is not necessary because the percent of change is not used as diagnostic criteria. A low-dose test, done with 1 mcg of cosyntropin, performs equally well for primary adrenal insufficiency and may be superior for diagnosing secondary adrenal insufficiency.[13] The test requires

TABLE 2
Diagnosis of Adrenal Insufficiency

Symptoms
Common: fatigue, weakness, anorexia, nausea, vomiting
Less common: abdominal pain, salt craving, diarrhea, constipation, syncope
Signs
Weight loss, cutaneous and mucosal pigmentation, hypotension, hypoglycemia
Laboratory test results*
Decreased sodium, bicarbonate, and chloride levels
Decreased basal levels of cortisol, no increase after ACTH or cosyntropin (Cortrosyn) administration
Decreased basal levels of aldosterone
Increased potassium level
Elevated ACTH levels in primary adrenal insufficiency
Mild to moderate increased calcium level (in 10 to 20 percent of patients)
Normocytic anemia (uncommon)

ACTH = adrenocorticotropic hormone.

**—In the early stages of adrenal insufficiency, laboratory test results may be normal.*

intravenous administration and careful timing of the cortisol level. The diagnosis of primary adrenal insufficiency can be confirmed by an increased plasma ACTH level.

The thyroid abnormalities and diabetes components of APS II are diagnosed in the conventional manner: thyrotropin secreting hormone and serum-free thyroxine are used to diagnose thyroid disease,[14] and the recommended diagnostic criteria for diabetes mellitus are based on a fasting blood glucose level.[15]

Concomitant diagnosis of primary adrenal insufficiency and thyroid disease or type 1 diabetes (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. Adrenal cortex antibodies often are found early in APS II, but the levels may decrease after a long duration of disease. 21-Hydroxylase antibodies are highly sensitive and specific for primary adrenal insufficiency of autoimmune origin.[16] Adrenal cortex antibodies or 21-hydroxylase antibodies are virtually always present with APS II because autoimmune adrenal insufficiency is required for the diagnosis. Thyroid peroxidase autoantibodies (80 to 90 percent of patients) and thyroglobulin autoantibodies (60 to 70 percent of patients) are detected in patients with Hashimoto's thyroiditis.[2] Islet cell antibodies can be demonstrated in about 80 percent of patients with new-onset type 1 diabetes.[2] Glutamic acid decarboxylase 65 autoantibodies are the marker with the highest diagnostic sensitivity for type 1 autoimmune diabetes.[2]

Because up to 50 percent of patients with autoimmune adrenal insufficiency may develop APS II, adults with the condition should be screened for thyroid disease and diabetes every five years.[17] On the other hand, only 1 percent of patients with thyroid disease will develop adrenal insufficiency; therefore, routine screening for other autoimmune diseases is not cost-effective in patients with thyroid disease.[8] Physicians should consider APS II if a patient develops a severe illness or the signs or symptoms of adrenal insufficiency listed in *Table 2*. In patients with type 1 diabetes, a sudden drop in insulin requirement may signal early adrenal insufficiency.

Treatment

Hormone therapy for component diseases is similar whether they occur in isolation or in association with other conditions. In patients with APS II and autoimmune hypothyroidism, it is essential to check adrenal function before initiating treatment for hypothyroidism. Initiation of thyroid hormone therapy in a patient with untreated adrenal insufficiency can precipitate a life-threatening adrenal crisis because the thyroxine stimulates increased metabolism of corticosteroids in the liver.[8,18]

When acute adrenal insufficiency is strongly suspected, therapy should not be delayed while waiting for laboratory test results. In patients with addisonian crisis, the initial goal is to reverse hypotension and electrolyte abnormalities, and to treat

shock when it occurs. Fluids (i.e., normal saline with 5% dextrose) should be given intravenously at twice the maintenance dose. Hydrocortisone 100 mg is given intravenously in appropriate doses. Some physicians prefer dexamethasone (Decadron; 2 to 4 mg depending on age) because the effect lasts 12 to 14 hours and the analogues do not affect steroid measurements during subsequent ACTH testing. The dose usually can be tapered over three days to a maintenance dose of 15 to 20 mg of hydrocortisone orally. To minimize weight gain and osteoporosis, the goal is to use the smallest dose that relieves the patient's symptoms. In patients with primary adrenal insufficiency, mineralocorticoid replacement with fludrocortisone (Florinef) 0.1 mg also should be given.[1]

Education is important because the patient must understand the need for lifelong medication and that the dose will need to be increased at times of stress or illness. Patients with adrenal insufficiency should carry a card with information on their current therapy and recommendations for treatment in case of emergency. A medical alert bracelet or necklace noting the condition should be worn. Patients should be directed to contact their doctors whenever they become ill.

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