This article describes types 1-4 autoimmune polyglandular syndromes that affect multiple endocrine organs, primarily the adrenal glands.

**What is Polyglandular Syndrome?**

Polyglandular or polyendocrine is a term referring to multiple endocrine glands. Autoimmune polyglandular or polyendocrine syndromes (APS types 1-4) are diseases involving multiple glands and sometimes other organs. Although these syndromes have been reported as long ago as 1908, the term APS was originally defined in 1980 by Blizzard, Maclaren and Neufeldt as involving a constellation of different autoimmune disorders, including adrenal insufficiency, Hashimoto’s thyroiditis, Graves’ disease, type 1 diabetes, and hypoparathyroidism.

The highest risk of APS exists in patients with autoimmune adrenal failure and individuals with a family history of polyglandular failure. Autoimmune adrenal insufficiency is a significant contributor to APS, occurring in APS types 1, 2, and 4.

**APECED**

Today type 1 APS is commonly referred to as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy or APECED. APECED is a rare autosomal recessive illness that classically occurs in children younger than 10 years, showing up first as a chronic condition of mucocutaneous or oral candidiasis and later progressing to hypoparathyroidism and primary adrenal insufficiency.

For a diagnosis of APECED at least two of these three conditions must be present. In about half of all patients, only two of these disorders are present, and disease progression is typically complete by age 20. Candidiasis, which is caused by infection with the fungus Candida albicans, usually occurs before the age of 5 and may affect the nails, skin, tongue and the mucous membranes. Systemic infection affecting the blood only occurs rarely and some patients may develop esophagitis, retrosternal pain, and epithelial cancer in the oral mucosa. Autoimmune hypoparathyroidism usually develops by age 10 in patients with APECED. When adrenal insufficiency occurs in patients with APECED it usually develops by age 15 years and affects 22-93 percent of patients. Adrenal antibodies usually are noted before signs of adrenal insufficiency occur. A related condition known as incomplete APS type 1 occurs in patients with candidiasis or hypoparathyroidism who have adrenal antibodies but no signs of adrenal insufficiency. These patients always go on to later develop Addison’s disease.

**Who Is Affected?**
Males and females are affected equally by APECED. Patients with APECED have been found to also occasionally develop keratoconjunctivitis, intestinal malabsorption, pancreatic insufficiency, alopecia, and type 1 diabetes. APECED has no known association with the immune system’s HLA antigens although there is an association with the autoimmune regulator or AIRE gene, which is located on the long arm of chromosome 21.

To date, 30 different mutations of the AIRE gene have been discovered that affect areas where the gene is expressed, such as the adrenals, pancreas, lymphoid tissue and gonads. Studies show that patients who first show signs of APECED at an earlier age are more likely to develop additional related autoimmune disorders and neoplasms.

**Adrenal Antibodies**

Nearly all patients with APECED who have adrenal antibodies progress to adrenal failure. Patients with APECED are also at high risk for pernicious anemia, hypogonadism, Sjogren’s syndrome, vitiligo, alopecia, autoimmune hepatitis, Turner’s syndrome, and malabsorption syndromes including celiac disease and atrophic gastritis. Celiac disease has been reported in 12.5 percent of people with APECED. The groups at highest risk for APECED include Iranian and Italian Jews and people from Finland and Sardinia. Worldwide, the presence of APS 1 is very low although the incidence is higher in the populations mentioned.

**APS Subtypes**

Type 2 APS or APS2, which is characterized by adrenal insufficiency along with one or more additional autoimmune endocrine disorders, was originally known as Schmidt’s syndrome. Although it may occur at any age, APS2 primarily occurs in middle-aged adults and women are affected about 3 times as often as men. The mean age of onset is 36 years. The most common second disorders include thyroid dysfunction, type 1 diabetes mellitus and pernicious anemia, APS2 has no association with the AIRE gene, but it is associated with various HLA antigens including DR3 and B8. In contrast to APECED, only about 20 percent of patients with APS2 who have adrenal antibodies develop adrenal failure. And approximately half of patients with APS2 report a family history of polyglandular failure. Studies show that about half of the patients presenting with autoimmune Addison’s disease go on to develop APS2.

Among patients with APS2, patients with initial conditions of diabetes are more likely to develop Addison’s disease. Among patients with APS2 who have thyroid disorders, patients with Graves’ disease usually develop thyroid disease before adrenal disease and patients with Hashimoto’s thyroiditis usually develop Addison’s disease before developing hypothyroidism.

Overall, in APS2 less than 1 percent of patients who initially present with autoimmune thyroid disease or type 1 diabetes go on to develop Addison’s disease. However, patients with diabetes who begin to experience unstable or poorly controlled glucose levels should
be tested for both adrenal and thyroid antibodies. Patients with APS2 often develop other autoimmune conditions although these disorders are less likely to occur in APS2 compared to APS1. These disorders include vitiligo, myasthenia gravis, thrombocytopenic purpura, Sjogren’s syndrome, rheumatoid arthritis, alopecia, hypergonadotropic hypogonadism, pernicious anemia, atrophic gastritis, hypophysitis, and primary antiphospholipid syndrome. In some cases, development of one of these other conditions is the first indication that the patient may also have APS.

Treatment for APS2 consists of individualized, lifelong hormone replacement therapy for the affected organs and routine monitoring of other endocrine organs since they can also become affected. Significant problems can occur if patients with a family history of APS who have one autoimmune endocrine disorder aren’t tested for other endocrine disorders. Because thyroxine replacement hormone used in hypothyroidism increases metabolism and the body’s needs for cortisol, treating hypothyroidism can worsen an undiagnosed condition of adrenal insufficiency in both humans and canines, particularly boxers (reported in 1995 by Kooistra et al, and reported in one of my boxers in 2005). A case of Addisonian Crisis precipitated by thyroxine therapy has been reported in a patient whose adrenal insufficiency had not yet been diagnosed. (Addisonian Crisis Precipitated by Thyroxine Therapy: A Complication of Type 2 Autoimmune Polyglandular Syndrome; Leland Graves, Robert Klein, and Ann Walling, South Med J 96(8):824-827, 2003)

APS type 3 occurs when patients with autoimmune thyroid diseases, including Hashimoto’s thyroiditis, Graves’ disease, idiopathic myxedema and euthyroid Graves’ disease, develop a second autoimmune condition, excluding autoimmune adrenal and parathyroid disorders. The second condition in APS3 is usually type 1 diabetes, atrophic gastritis, pernicious anemia, vitiligo, alopecia, or myasthenia gravis. Patients with APS3 may later progress to APS2 if they develop an autoimmune adrenal or parathyroid condition.

APS type 4 occurs when patients develop two or more autoimmune endocrine conditions that cannot be classified as APS types 1, 2, or 3. An example would be a patient with diabetes who develops an autoimmune growth hormone deficiency or a patient with adrenal insufficiency who develops celiac disease.

Theories regarding the development of APS include: shared autoantigens by multiple endocrine organs, an environmental agent targeting various endocrine antigens, and genetic mutations. Because there are no spontaneous animal models for APS, there is no definitive theory to explain their occurrence.