TABLE 409-3 CLINICAL FEATURES AND RECOMMENDED FOLLOW-UP FOR APS-1 AND APS-2

Component Disease	Recommended Evaluation
APS-1	
Addison's disease	Sodium, potassium, ACTH, cortisol, 21- and 17-hydroxylase autoantibodies
Diarrhea	History
Ectodermal dysplasia	Physical examination
Hypoparathyroidism	Serum calcium, phosphate, PTH
Hepatitis	Liver function tests
Hypothyroidism/ Graves' disease	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies and anti-TSH receptor Ab
Male hypogonadism	FSH/LH, testosterone
Malabsorption	Physical examination, anti-IL-17 and anti-IL-22 autoantibodies
Mucocutaneous candidiasis	Physical examination, mucosal swab, stool samples
Obstipation	History
Ovarian failure	FSH/LH, estradiol
Pernicious anemia	CBC, vitamin B_{12} levels
Splenic atrophy	Blood smear for Howell-Jolly bodies; platelet count; ultrasound if positive
Type 1 diabetes	Glucose, hemoglobin A_{1c}, diabetes-associated autoantibodies (insulin, GAD65, IA-2, ZnT8)
APS-2	
Addison's disease	21-Hydroxylase autoantibodies, ACTH stimulation testing if positive
Alopecia	Physical examination
Autoimmune hyper- or hypothyroidism	TSH; thyroid peroxidase and/or thyroglobulin autoantibodies, anti-TSH receptor Ab
Celiac disease	Transglutaminase autoantibodies; small intestine biopsy if positive
Cerebellar ataxia	Dictated by signs and symptoms of disease
Chronic inflammatory demyelinating polyneuropathy	Dictated by signs and symptoms of disease
Hypophysitis	Dictated by signs and symptoms of disease, anti-Pit1 autoantibody
Idiopathic heart block	Dictated by signs and symptoms of disease
IgA deficiency	IgA level
Myasthenia gravis	Dictated by signs and symptoms of disease, antiacetylcholinesterase Ab
Myocarditis	Dictated by signs and symptoms of disease
Pernicious anemia	Anti–parietal cell autoantibodies
	CBC, vitamin B_{12} levels if positive
Serositis	Dictated by signs and symptoms of disease
Stiff man syndrome	Dictated by signs and symptoms of disease
Vitiligo	Physical examination, NALP-1 polymorphism

Abbreviations: Ab, antibody; ACTH, adrenocorticotropic hormone; APS, autoimmune polyendocrine syndrome; CBC, complete blood count; FSH, follicle-stimulating hormone; IL, interleukin; LH, luteinizing hormone; PTH, parathyroid hormone; TSH, thyroid-stimulating hormone.

APS-2

APS-2 (OMIM 269200) is more common than APS-1 with a prevalence of 1 in 100,000. It has a gender bias and occurs more often in female patients with a ratio of at least 3:1 compared to male patients. In contrast to APS-1, APS-2 often has its onset in adulthood with a peak incidence between 20 and 60 years of age. It shows a familial, multigenerational heritage (Table 409-2). The presence of two or more of the following endocrine deficiencies in the same patient defines the presence of APS-2: primary adrenal insufficiency (Addison's disease; 50–70%), Graves' disease or autoimmune thyroiditis (15–69%), type 1 diabetes mellitus (T1D; 40–50%), and primary hypogonadism. Frequently associated autoimmune conditions include celiac disease (3–15%), myasthenia gravis, vitiligo, alopecia, serositis, and pernicious anemia. These conditions occur with increased frequency in affected patients but are also are found in their family members (Table 409-3).

Genetic Considerations The overwhelming risk factor for APS-2 has been localized to the genes in the human lymphocyte antigen complex on chromosome 6. Primary adrenal insufficiency in APS-2, but not APS-1, is strongly associated with both HLA-DR3 and HLA-DR4. Other class I and class II genes and alleles, such as HLA-B8, HLA-DQ2 and HLA-DQ8, and HLA-DR subtype such as DRB1*0404, appear to contribute to organ-specific disease susceptibility (Table 409-4). HLA-B8- and HLA-DR3-associated illnesses include selective IgA deficiency, juvenile dermatomyositis, dermatitis herpetiformis, alopecia, scleroderma, autoimmune thrombocytopenia purpura, hypophysitis, metaphyseal osteopenia, and serositis.

Several other immune genes have been proposed to be associated with Addison's disease and therefore with APS-2 (Table 409-3). The "5.1" allele of a major histocompatibility complex (MHC) gene is an atypical class I HLA molecule MIC-A. The MIC-A5.1 allele has a very strong association with Addison's disease that is not accounted for by linkage disequilibrium with DR3 or DR4. Its role is complicated because certain HLA class I genes can offset this effect. PTPN22 codes for a polymorphism in a protein tyrosine phosphatase, which acts on intracellular signaling pathways in both T and B lymphocytes. It has been implicated in T1D, Addison's disease, and other autoimmune conditions. CTLA4 is a receptor on the T cell surface that modulates the activation state of the cell as part of the signal 2 pathway. Polymorphisms of this gene appear to cause downregulation of the cell surface expression of the receptor, leading to decreased T cell activation and proliferation. This appears to contribute to disease in Addison's disease and potentially other components of APS-2. Allelic variants of the IL-2Rα are linked to development of T1D and autoimmune thyroid disease and could contribute to the phenotype of APS-2 in certain individuals.

Diagnosis When one of the component disorders is present, a second associated disorder occurs more commonly than in the general population (Table 409-3). There is controversy as to which tests to use and how often to screen individuals for disease. A strong family history of autoimmunity should raise suspicion in an individual with an initial component diagnosis. The development of a rarer form of autoimmunity, such as Addison's disease, should prompt more extensive screening for other linked disorders compared to the diagnosis of autoimmune thyroid disease, which is relatively common.

Circulating autoantibodies, as previously discussed, can precede the development of disease by many years but would allow the clinician to follow the patient and identify the disease onset at its earliest time point (Tables 409-3 and 409-4). For each of the endocrine components of the disorder, appropriate autoantibody assays are listed and, if positive, should prompt physiologic testing to diagnose clinical or subclinical disease. For Addison's disease, antibodies to 21-hydroxylase antibodies are highly diagnostic for risk of adrenal insufficiency. However, individuals may take many years to develop overt hypoadrenalism. Screening of 21-hydroxylase antibody–positive patients can be performed measuring morning ACTH and cortisol on a yearly basis. Rising ACTH values over time or low morning cortisol in association with signs or symptoms of adrenal insufficiency should prompt testing via the cosyntropin stimulation test (Chap. 406). T1D can be screened for by measuring autoantibodies including anti-insulin, anti-GAD65, anti-IA-2, and anti-ZnT8. Risk for progression to disease can be based on the number of antibodies, and in some cases the titer (insulin autoantibody), as well as other metabolic factors (impaired oral glucose tolerance test). National Institutes of Health–sponsored trial groups such as Type 1 Diabetes TrialNet are screening first- and second-degree family members for these autoantibodies and identifying prediabetic individuals who may qualify for intervention trials to change the course of the disease prior to onset.