TABLE 409-4 APS-2 AND OTHER POLYENDOCRINE DISORDER ASSOCIATIONS

Disease	HLA Association	Initiating Factor	Mechanism	Autoantigen
Graves' Disease	DR3	Iodine Anti-CD52	Antibody	TSH receptor
Myasthenia gravis	DR3, DR7	Thymoma Penicillamine	Antibody	Acetylcholine receptor
Anti-insulin receptor	?	SLE or other autoimmune disease	Antibody	Insulin receptor
Hypoparathyroidism	?	?	Antibody	Cell surface inhibitor
Insulin autoimmune syndrome	DR4, DRB1*0406	Methimazole Sulfhydryl-containing drugs	Antibody	Insulin
Celiac disease	DQ2/DQ8	Gluten diet	T cell	Transglutaminase
Type 1 diabetes	DR3/DR4 DQ2/DQ8	? Congenital rubella	T cell	Insulin, GAD65, IA-2, ZnT8, IGRP
Addison's disease	DR3/DR4 DRB1*0404	Unknown	T cell	21-Hydroxylase P450-5cc
Thyroiditis	DR3/DQB1*0201 DQA1*0301	Iodine Interferon α	T cell	Thyroglobulin Thyroid peroxidase
Pernicious anemia	?	?	T cell	Intrinsic factor H+/K+ ATPase
Vitiligo	?	Melanoma Antigen Immunization	?	Melanocyte
Chromosome dysgenesis–trisomy 21 and Turner's syndrome	DQA1*0301	?	?	Thyroid, islet, transglutaminase
Hypophysitis	?	Pit-1, TDRD6	?	Pituitary, Pit-1

Abbreviations: APS, autoimmune polyendocrine syndrome; SLE, systemic lupus erythematosus; TSH, thyroid-stimulating hormone.

Screening tests for thyroid disease can include anti–thyroid peroxidase (TPO) or anti-thyroglobulin autoantibodies or anti-TSH receptor antibodies for Graves' disease. Yearly measurements of TSH can then be used to follow these individuals. Celiac disease can be screened for using the anti–tissue transglutaminase (tTg) antibody test. For those <20 years of age, testing every 1–2 years should be performed, whereas less frequent testing is indicated after the age of 20 because the majority of individuals who develop celiac disease have the antibody earlier in life. Positive tTg antibody test results should be confirmed on repeat testing, followed by small-bowel biopsy to document pathologic changes of celiac disease. Many patients have asymptomatic celiac disease that is nevertheless associated with osteopenia and impaired growth. If left untreated, symptomatic celiac disease has been reported to be associated with an increased risk of gastrointestinal malignancy, especially lymphoma.

The knowledge of the particular disease associations should guide other autoantibody or laboratory testing. A complete history and physical examination should be performed every 1–3 years including CBC, metabolic panel, TSH, and vitamin B_{12} levels to screen for most of the possible abnormalities. More specific tests should be based on specific findings from the history and physical.

TREATMENT APS-2

With the exception of Graves' disease, the management of each of the endocrine components of APS-2 involves hormone replacement and is covered in detail in the chapters on adrenal **(Chap. 406)**, thyroid **(Chap. 405)**, gonadal **(Chaps. 411 and 412)**, and parathyroid disease **(Chap. 424)**. As noted for APS-1, adrenal insufficiency can be masked by primary hypothyroidism and should be considered and treated as discussed above. In patients with T1D, decreasing insulin requirements or hypoglycemia, without obvious secondary causes, may indicate the emergence of adrenal insufficiency. Hypocalcemia in APS-2 patients is more likely due to malabsorption than hypoparathyroidism.

Immunotherapy for autoimmune endocrine disease has been reserved for T1D, for the most part, reflecting the lifetime burden of the disease for the individual patient and society. Although several immunotherapies (e.g., modified anti-CD3, rituximab, abatacept) can prolong the honeymoon phase of T1D, none has achieved long-term success. Active research using new approaches and combination therapy may change the treatment of this disease or other autoimmune conditions that share similar pathways. Furthermore, treatment of subclinical disease diagnosed by the presence of autoantibodies may provide a mechanism to preempt the development of overt disease and is the subject of active basic and clinical research.

IPEX

*I*mmune dysregulation, *p*olyendocrinopathy, *e*nteropathy, and *X*-linked disease (IPEX; OMIM 304790) is a rare X-linked recessive disorder. The disease onset is in infancy and is characterized by severe enteropathy, T1D, and skin disease, as well as variable association with several other autoimmune disorders. Many infants die within the first days of life, but the course is variable, with some children surviving for 12–15 years. Early onset of T1D, often at birth, is highly suggestive of the diagnosis because nearly 80% of IPEX patients develop T1D. Although treatment of the individual disorders can temporarily improve the situation, treatment of the underlying immune deficiency is required and includes immunosuppressive therapy generally followed by hematopoietic stem cell transplantation. Transplantation is the only life-saving form of therapy and can be fully curative by normalizing the imbalanced immune system found in this disorder.