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Autoimmune

Polyendocrine Syndromes Polyglandular deficiency syndromes have been given many differ ent names, reflecting the wide spectrum of disorders that have been associated with these syndromes and the heterogeneity of their clinical presentations. The name used in this chapter for this group of disorders is autoimmune polyendocrine syndrome (APS). In general, these disor ders are divided into two major categories, APS type 1 (APS-1) and APS type 2 (APS-2). Some groups have further subdivided APS-2 into APS type 3 (APS-3) and APS type 4 (APS-4) depending on the type of autoimmunity involved. For the most part, this additional classification does not clarify our understanding of disease pathogenesis or preven tion of complications in individual patients. Importantly, there are many nonendocrine disease associations included in these syndromes, suggesting that although the underlying autoimmune disorder predomi nantly involves endocrine targets, it does not exclude other tissues. The disease associations found in APS-1 and APS-2 are summarized in Table 401-1. Understanding these syndromes and their disease manifestations can lead to early diagnosis and treatment of additional disorders in patients and their family members. TABLE 401-1 Disease Associations with Autoimmune Polyendocrine Syndromes AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 1 AUTOIMMUNE POLYENDOCRINE SYNDROME TYPE 2 OTHER AUTOIMMUNE POLYENDOCRINE DISORDERS Endocrine Endocrine IPEX (immune dysfunction polyendocrinopathy X-linked) Addison’s disease Addison’s disease Thymic tumors Hypoparathyroidism Type 1 diabetes Anti-insulin receptor antibodies Hypogonadism Graves’ disease or autoimmune thyroiditis POEMS syndrome Graves’ disease or Hypogonadism Insulin autoimmune syndrome (Hirata’s syndrome) autoimmune thyroiditis Type 1 diabetes Adult combined pituitary hormone deficiency (CPHD) with anti-Pit1 autoantibodies Kearns-Sayre syndrome DIDMOAD syndrome Nonendocrine Nonendocrine Congenital rubella associated with thyroiditis and/or diabetes Mucocutaneous Celiac disease, dermatitis herpetiformis candidiasis Chronic active Pernicious anemia hepatitis Pernicious anemia Vitiligo Vitiligo Alopecia Asplenism Myasthenia gravis Ectodermal dysplasia IgA deficiency Alopecia Parkinson’s disease Malabsorption Idiopathic thrombocytopenia syndromes IgA deficiency Abbreviations: DIDMOAD,

diabetes insipidus, diabetes mellitus, progressive bilateral optic atrophy, and sensorineural deafness; POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes. Note: Italics denote less common disorders.

■ ■APS-1 APS-1 (Online Mendelian Inheritance in Man [OMIM] 240300) has also been called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED). Mucocutaneous candidiasis, hypoparathyroid ism, and Addison's disease form the three major components of this disorder. However, as summarized in Table 401-1, many other organ systems can be involved over time. APS-1 is rare, with <500 cases reported in the literature.

The classical form of APS-1 is an autosomal recessive disorder caused by mutations in the AIRE gene (autoimmune regulator gene) found on chromosome 21. This gene is most highly expressed in thy mic medullary epithelial cells (mTECs) where it controls the expression of tissue-specific self-antigens (e.g., insulin). Deletion of this regulator leads to decreased expression of tissue-specific self-antigens and is hypothesized to allow autoreactive T cells to avoid central deletion, which normally occurs during T-cell maturation in the thymus. The AIRE gene is also expressed in epithelial cells found in peripheral lymphoid organs, but its role in these extrathymic cells remains con troversial. To date, >100 mutations have been described in this gene, and there is a higher frequency within certain ethnic groups includ ing Iranian Jews, Sardinians, Finns, Norwegians, and Irish. Recently, several autosomal dominant mutations have been identified and are localized primarily in the PHD1 domain of the AIRE gene, rather than the CARD region, where the autosomal recessive mutations have been found. Individuals with this nonclassical form of APS-1 may have a later onset of symptoms and less aggressive disease, without the full spectrum of autoimmune components being expressed. Autoimmune Polyendocrine Syndromes CHAPTER 401 Clinical Manifestations Classical APS-1 develops very early in life, often in infancy (Table 401-2). Chronic mucocutaneous candi diasis without signs of systemic disease is often the first manifesta tion. It affects the mouth and nails more frequently than the skin and esophagus. Chronic oral candidiasis can result in atrophic disease with areas suggestive of leukoplakia, which can pose a risk for future carcinoma. The etiology is associated with anticytokine autoantibodies (anti-interleukin [IL] 17A, IL-17F, and IL-22) related to T helper (TH) 17 T cells and depressed production of these cytokines by peripheral blood mononuclear cells. Hypoparathyroidism usually develops next, followed by adrenal insufficiency. The time from development of one component of the disorder to the next can be many years, and the order of disease appearance is variable. Chronic candidiasis is nearly always present and is not very respon sive to treatment. Hypoparathyroidism is found in >85% of cases, and Addison's disease is found in nearly 80%. Gonadal failure appears to affect women more than men (70 vs 25%, respectively), and hypo plasia of the dental enamel also occurs frequently (77% of patients). TABLE 401-2 Comparison of APS-1 and APS-2 APS-1 APS-2 Early onset: infancy Later onset Siblings often affected and at risk Multigenerational Equivalent sex distribution Females > males affected Monogenic: AIRE gene, chromosome 21, autosomal recessive Polygenic: HLA, MICA, PTNP22, CTLA4 Not HLA associated for entire syndrome, some specific component risk DR3/DR4 associated; other HLA class III gene associations noted Autoantibodies to type 1 interferons and IL-17 and IL-22 No autoantibodies to cytokines Autoantibodies to specific target organs Autoantibodies to specific target organs Asplenism No defined immunodeficiency Mucocutaneous candidiasis Association with other nonendocrine immunologic disorders like myasthenia gravis and idiopathic thrombocytopenic purpura Abbreviations: APS, autoimmune polyendocrine syndrome; HLA, human leukocyte antigen; IL, interleukin.

Other endocrine disorders that occur less frequently include type 1 diabetes (23%) and autoimmune thyroid disease (18%). Nonendocrine manifestations that present less frequently include alopecia (40%), vitiligo (26%), intestinal malabsorption (18%), pernicious anemia (31%), chronic active hepatitis (17%), and nail dystrophy. An unusual and debilitating manifestation of the disorder is the development of refractory diarrhea/obstipation that may be related to autoantibodymediated destruction of enterochromaffin or enterochromaffin-like cells. The incidence rates for many of these disorders peak in the first or second decade of life, but the individual disease components con tinue to emerge over time. Therefore, prevalence rates may be higher than originally reported.

PART 12 Endocrinology and Metabolism Diagnosis The diagnosis of APS-1 is usually made clinically when two of the three major component disorders are found in an indi vidual patient. Siblings of individuals with APS-1 should be considered affected even if only one component disorder has been detected due to the known inheritance of the syndrome. Genetic analysis of the AIRE gene should be undertaken to identify mutations. Detection of anti–interferon α and anti–interferon ω antibodies can identify nearly 100% of cases with APS-1. The autoantibody arises independent of the type of AIRE gene mutation and is not found in other autoimmune disorders. Diagnosis of each underlying disorder should be done based on their typical clinical presentations (Table 401-3). Mucocutaneous candidiasis may present throughout the gastrointestinal tract, and it may be detected in the oral mucosa or from stool samples. Evaluation by a gastroenterologist to examine the esophagus for candidiasis or secondary stricture may be merited based on symptoms. Other gas trointestinal manifestations of APS-1, including malabsorption and obstipation, may also bring these young patients to the attention of gastroenterologists for first evaluation. Specific physical examination findings of hyperpigmentation, vitiligo, alopecia, tetany, and signs of hyper- or hypothyroidism should be considered as signs of develop ment of component disorders. The development of disease-specific autoantibody assays can help confirm disease and also detect risk for future disease. For example, where possible, detection of anticytokine antibodies to IL-17 and IL-22 would confirm the diagnosis of mucocutaneous candidiasis due to APS-1. The presence of anti-21-hydroxylase antibody or anti17-hydroxylase antibody (which may be found more commonly in adrenal insufficiency associated with APS-1) would confirm the pres ence or risk for Addison’s disease. Other autoantibodies found in type 1 diabetes (e.g., anti-GAD65), pernicious anemia, and other component conditions should be screened for on a regular basis (6- to 12-month intervals depending on the age of the subject). Laboratory tests, including a complete metabolic panel, phospho rous and magnesium, thyroid-stimulating hormone (TSH), adreno corticotropic hormone (ACTH; morning), hemoglobin A1c, plasma vitamin B12 level, and complete blood count with peripheral smear looking for Howell-Jolly bodies (asplenism), should also be performed at these time points. Detection of abnormal physical findings or test results should prompt subsequent examinations of the relevant organ system (e.g., presence of Howell-Jolly bodies indicates need for ultra sound of spleen). TREATMENT APS-1 Therapy of individual disease components is carried out as outlined in other relevant chapters. Replacement of deficient hormones (e.g., adrenal, pancreas, ovaries/testes) will treat most of the endo crinopathies noted. Several unique issues merit special emphasis. Adrenal insufficiency can be masked by primary hypothyroidism by prolonging the half-life of cortisol. The caveat therefore is that replacement therapy with thyroid hormone can precipitate an adrenal crisis in an undiagnosed individual. Hence, all patients with hypothyroidism and the possibility of APS should be screened

TABLE 401-3 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 B12 levels Splenic atrophy Blood smear for Howell-Jolly bodies; platelet count; ultrasound if positive Type 1 diabetes Glucose, hemoglobin A1c, 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 B12 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. for adrenal insufficiency to allow treatment with glucocorticoids prior to the initiation of thyroid hormone replacement. Treatment of mucocutaneous candidiasis with ketoconazole in an individual with subclinical adrenal insufficiency may also precipitate adrenal crisis. Furthermore, mucocutaneous candidiasis may be difficult to eradicate entirely. Severe cases of disease involvement may require systemic immunomodulatory therapy, but this is not commonly needed. ■ ■APS-2 APS-2 (OMIM 269200) is more common than APS-1, with a preva lence of 1–2 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 401-2). 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 dis ease; 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 found in their family members (Table 401-3). Genetic Considerations The overwhelming risk factor for APS-2 has been localized to the genes in the human lymphocyte antigen (HLA) 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 subtypes such as DRB1∗04:04, appear to contribute to organ-specific disease susceptibility (Table 401-4). HLA-B8- and HLA-DR3-associated

ill nesses include selective IgA deficiency, juvenile dermatomyositis, der matitis 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 401-3). 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 con ditions. CTLA4 is a receptor on the T-cell surface that modulates the activation state of the cell as part of the signal 2 pathway (i.e., binding to CD80/86 on antigen presenting cells). Polymorphisms of this gene TABLE 401-4 APS-2 and Other Polyendocrine Disorder Associations DISEASE HLA ASSOCIATION INITIATING FACTOR MECHANISM AUTOANTIGEN Graves' disease DR3 Iodine Anti-CD52 Myasthenia gravis DR3, DR7 Thymoma Penicillamine 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 Celiac disease DQ2/DQ8 Gluten diet T cell Transglutaminase Type 1 diabetes DR3/DR4 DQ2/DQ8 ? Congenital rubella Addison's disease DR3/DR4 DRB1*0404 Unknown T cell 21-Hydroxylase P450-5cc Thyroiditis DR3/DQB1*0201 DQA1* 0301 Iodine Interferon α Pernicious anemia ? ? T cell Intrinsic factor H+/K+ ATPase Vitiligo ? Melanoma Antigen Immunization 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.

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 Addison's disease and potentially other com ponents of APS-2. Allelic variants of the IL-2Rα are linked to develop ment 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 401-3). 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 autoimmu nity, such as Addison's disease, should prompt more extensive screen ing for other linked disorders, as ~50% of Addison's disease patients develop another autoimmune disease during their lifetime. Autoimmune Polyendocrine Syndromes CHAPTER 401 Circulating autoantibodies, as previously discussed, can precede the development of clinical disease by many years but would allow the clinician to follow the patient and identify the disease onset at its earliest time point (Tables 401-3 and 401-4). 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 symptoms of 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. 398). T1D can be screened for by measuring autoantibodies directed against insulin, GAD65, IA-2, and ZnT8. Risk for progression to disease is based on the number of antibodies (≥2 islet autoantibodies with nor mal glucose tolerance is now defined as stage 1 of T1D as the lifetime risk for developing clinical symptoms is nearly 100%) and metabolic factors (impaired oral glucose tolerance test). Many efforts are ongo ing and underway to screen relatives of T1D patients and those in the general population for islet autoantibodies to identify individuals with Antibody TSH receptor Antibody Acetylcholine receptor Antibody Insulin T cell Insulin, GAD65, IA-2, ZnT8, IGRP T cell Thyroglobulin Thyroid peroxidase ? Melanocyte

preclinical disease who may elect to have treatment with teplizumab, anti-CD3 monoclonal antibody, to delay the clinical onset of diabetes.

Screening tests for thyroid disease can include anti–thyroid peroxi dase (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 major ity 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, and osteoporosis later in life. PART 12 Endocrinology and Metabolism 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 complete blood count, metabolic panel, TSH, and vitamin B12 levels to screen for most of the possible abnormalities. More specific tests should be based on specific findings from the history and physical examination. TREATMENT APS-2 With the exception of Graves' disease, the management of each endocrine component of APS-2 involves hormone replacement and is covered in detail in the chapters on adrenal (Chap. 398), thyroid (Chap. 394), gonadal (Chaps. 403 and 404), and para thyroid diseases (Chap. 422). As noted for APS-1, adrenal insuf ficiency 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 insuf ficiency. Hypocalcemia in APS-2 patients is more likely due to malabsorption, potentially from undiagnosed celiac disease, 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, alefacept, low-dose antithymocyte globulin, TNF-α inhibitors, and JAK inhibitors) can prolong the honeymoon phase of T1D, none has achieved long-term success. Notably, the antiCD3 monoclonal antibody (teplizumab) does delay the onset of clinical diabetes by an average of 3 years when

administered to individuals with stage 2 T1D (e.g., those with autoantibodies and impaired glucose tolerance) and is now approved for clinical use in the United States. Active basic and clinical research using novel therapies and combinations may change the treatment landscape of this disease and other autoimmune conditions that share similar pathways. ■ ■IMMUNE CHECKPOINT INHIBITOR–INDUCED ENDOCRINE AUTOIMMUNITY Therapies that block immune checkpoints, such as programmed cell death protein 1 (PD-1), its ligand (PD-L1), or CTLA-4, are beneficial immunotherapies for many advanced-stage cancers. These immune checkpoint inhibitors (ICIs) block negative immune regulation, thereby allowing for an immune response directed against tumor cells. However, immune-related adverse events also occur, especially autoimmunity directed toward self-tissues. ICI-induced T1D, thy roid disease, hypophysitis, and adrenal insufficiency have all been reported with these therapies and in combination. Hypothyroidism

occurs in ~10% and T1D in 1–2% of those receiving monoclonal antibodies directed against PD-1 or PD-L1, and hypophysitis and adrenal insufficiency occur in <1% of treated patients. These autoim mune side effects can develop during or after therapy, mostly within a few weeks to months following the start of therapy. ICI-induced T1D has a very rapid onset, presents with diabetic ketoacidosis, is permanent, and requires lifelong exogenous insulin therapy for treat ment. There is a strong genetic association, with HLA-DR4 being present in ~70% of patients, and islet autoantibodies may be present at diagnosis. The pathogenesis is immune mediated as T lymphocyte infiltration has been documented in the pancreatic islets of an ICIT1D patient. Determining the mechanisms of autoimmune disease development following ICI therapies and developing biomarkers to stratify risk for autoimmune side effects prior to therapy are active areas of research. ■ ■IPEX Immune dysregulation, polyendocrinopathy, enteropathy, 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 sugges tive 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 fol lowed 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. IPEX is caused by mutations in the FOXP3 gene, which is also mutated in the Scurfy mouse, an animal model that shares much of the same phenotype of IPEX patients. The FOXP3 transcription fac tor is expressed in regulatory T cells designated CD4+CD25+FOXP3+ (Treg). Lack of this factor causes a profound deficiency of this Treg population and results in rampant autoimmunity due to the lack of peripheral tolerance normally provided by these cells. Certain muta tions may lead to varying forms of expression of the full syndrome, and there are rare cases where the FOXP3 gene is intact but other genes involved in this pathway (e.g., CD25, IL-2Rα) may be causative. Future therapy with autologous CD4+ T cells transfected with a func tioning FOXP3 gene may offer a better long-term outcome than has been seen in those treated with stem cell transplantation. ■ ■THYMIC TUMORS Thymomas and thymic hyperplasia are associated with several auto immune diseases, with the most common being myasthenia gravis (44%) and red cell aplasia (20%). Graves’ disease, T1D, and Addison’s disease may also be associated with thymic tumors. Patients with myasthenia gravis and thymoma may have unique anti–acetylcholine receptor autoantibodies. Most thymomas lack AIRE expression within the thymoma, and this could

be a potential factor in the development of autoimmunity. In support of this concept, thymoma is the one other disease with “frequent” development of anticytokine antibodies and mucocutaneous candidiasis in adults. The majority of tumors are malignant, and temporary remissions of the autoimmune condition can occur with resection of the tumor. ■ ■ANTI-INSULIN RECEPTOR ANTIBODIES This is a very rare disorder where severe insulin resistance (type B) is caused by the presence of anti-insulin receptor antibodies. It is associated with acanthosis nigricans, which can also be associated with other forms of less severe insulin resistance. About one-third of patients have an associated autoimmune illness such as systemic lupus erythematosus or Sjögren’s syndrome. Therefore, the presence of anti nuclear antibodies, elevated erythrocyte sedimentation rate, hyper globulinemia, leukopenia, and hypocomplementemia may accompany

the presentation. The presence of anti-insulin receptor autoantibodies leads to marked insulin resistance, requiring >100,000 units of insulin to be given daily with only partial control of hyperglycemia. Patients can also have severe hypoglycemia due to partial activation of the insulin receptor by the antibody. The course of the disease is variable, and several patients have had spontaneous remissions. A therapeutic approach that targets B lymphocytes, including rituximab, cyclophosphamide, and pulse steroids, has been validated in follow-on case reports to induce remission of the disease. ■ ■INSULIN AUTOIMMUNE SYNDROME (HIRATA’S SYNDROME) The insulin autoimmune syndrome, associated with Graves’ disease and methimazole therapy (or other sulfhydryl-containing medications), is of particular interest due to a remarkably strong association with a specific HLA haplotype. Such patients with elevated titers of anti-insulin antibodies frequently present with hypoglycemia. In Japan, the disease is restricted to HLA-DR4-positive individuals with DRB1∗04:06, while Caucasian patients predominantly have DRB1∗04:03 (which is related to DRB1∗04:06). In Hirata’s syndrome, the anti-insulin antibodies are often polyclonal. Discontinuation of the medication generally leads to resolution of the syndrome over time. There are very rare cases of insulin autoimmune syndrome not associated with sulfhydryl-containing medications that result in profound, life-threatening hypoglycemia. Treatment involves treating the underlying condition that causes anti-insulin antibodies, such as a B lymphocyte lymphoma (tend to have monoclonal insulin antibodies) or systemic lupus erythematosus. As hypoglycemia is profound when elevated titers of high-affinity insulin antibodies bind secreted insulin and then release it into circulation, treatment that begins with highdose glucocorticoids and rituximab to target B lymphocytes has been shown to be effective. ■ ■POEMS SYNDROME POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes; also known as Crow-Fukase syndrome; OMIM 192240) patients usually present with a progressive sensorimotor polyneuropathy, diabetes mellitus (50%), primary gonadal failure (70%), and a plasma cell dyscrasia with sclerotic bony lesions. Associated findings can be hepatosplenomegaly, lymphadenopathy, and hyperpigmentation. Patients often present in the fifth to sixth decade of life and have a median survival after diagnosis of <3 years. The syndrome is assumed to be secondary to circulating immunoglobulins, but patients have excess vascular endothelial growth factor as well as elevated levels of other inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor α. Patients have been treated with thalidomide, and more recently lenalidomide, leading to a decrease in vascular endothelial growth factor. Hyperglycemia responds to small, subcutaneous doses of insulin. The hypogonadism is due to primary gonadal disease with elevated plasma levels of follicle-stimulating hormone and luteinizing hormone. Temporary resolution of the features of POEMS, including normalization of blood glucose, may occur after radiotherapy for localized plasma cell lesions of bone or after chemotherapy, lenalidomide and dexamethasone, or autologous stem

cell transplantation. ■ ■OTHER DISORDERS Other diseases can exhibit polyendocrine deficiencies, including Kearns-Sayre syndrome, DIDMOAD syndrome (diabetes insipidus, diabetes mellitus, progressive bilateral optic atrophy, and sensorineural deafness; also termed Wolfram's syndrome), Down's syndrome or trisomy 21 (OMIM 190685), Turner's syndrome (monosomy X, 45,X0), and congenital rubella. Kearns-Sayre syndrome (OMIM 530000) is a rare mitochondrial DNA disorder characterized by myopathic abnormalities leading to ophthalmoplegia and progressive weakness in association with several endocrine abnormalities, including hypoparathyroidism, primary

gonadal failure, diabetes mellitus, and hypopituitarism. Crystalline mitochondrial inclusions are found in muscle biopsy specimens, and such inclusions have also been observed in the cerebellum. Antiparathyroid antibodies have not been described; however, antibodies to the anterior pituitary gland and striated muscle have been identified, and the disease may have autoimmune components. These mitochondrial DNA mutations occur sporadically and do not appear to be associated with a familial syndrome.

Wolfram's syndrome (OMIM 222300, chromosome 4; OMIM 598500, mitochondrial) is a rare autosomal recessive disease that is also called DIDMOAD. Neurologic and psychiatric disturbances are prominent in most patients and can cause severe disability. The disease is caused by defects in the Wolfram syndrome 1 (WFS1) gene, which encodes a 100-kDa transmembrane protein that has been localized to the endoplasmic reticulum and is found in neuronal and neuroendocrine tissue. Its expression induces ion channel activity with a resultant increase in intracellular calcium and may play an important role in intracellular calcium homeostasis. Wolfram's syndrome appears to be a slowly progressive neurodegenerative process, and there is nonautoimmune selective destruction of the pancreatic beta cells. Diabetes mellitus with an onset in childhood is usually the first manifestation. Diabetes mellitus and optic atrophy are present in all reported cases, but expression of the other features is variable. Treatments targeting endoplasmic reticulum dysfunction are being tested and may be a bridge until gene therapy can be developed to treat the most severely affected cases. Autoimmune Polyendocrine Syndromes CHAPTER 401 Down's syndrome, or trisomy 21 (OMIM 190685), is associated with the development of T1D, thyroiditis, and celiac disease. Patients with Turner's syndrome also appear to be at increased risk for the development of thyroid disease and celiac disease. It is recommended to screen patients with trisomy 21 and Turner's syndrome for associated autoimmune diseases on a regular basis. ■ ■GLOBAL CONSIDERATIONS Identification of these syndromes requires access to central laboratories with the ability to detect unique autoantibodies and to sequence the specific genes that may underlie these disorders. Early recognition of the clinical features of these disorders and timely referral and/or consultation with tertiary care centers to confirm the diagnosis and initiate therapy are important to improving outcomes. The AIRE recessive gene mutations found in APS-1 were originally described in high frequency in several populations including Finns, Iranian Jews, Sardinians, Norwegians, and Irish. Although individuals from many other countries have now been found to have these mutations and the newly identified dominant AIRE gene mutations, understanding the frequency in the background population may raise the clinician's level of suspicion for these rare disorders. Hirata's syndrome was originally reported in Japanese populations but also may be found in other populations, as noted. ■ ■FURTHER READING
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