

17. Immunologic endocrine disorders

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Immune-mediated tissue destruction or dysregulation is the cause of multiple common, as well as rare, endocrine disorders including type 1 diabetes, Graves' disease, Hashimoto thyroiditis, and Addison's disease. Each of these disorders can be divided into a series of stages beginning with genetic susceptibility, environmental triggering events, and active autoimmunity, followed by metabolic abnormalities with overt disease. Common genetic susceptibility is suggested by the clustering of a series of disorders in the same individual and his or her family. A major portion of the genetic susceptibility lies in the HLA region, but for several disorders, mutation of transcription factors underlies disease susceptibility (eg, X-linked polyendocrinopathy, immune deficiency and diarrhea, and autoimmune polyendocrine syndrome type 1). With improving immunogenetic and pathogenic understanding, type 1A diabetes is now predictable, and excellent autoantibody screening assays are available. This knowledge, combined with studies in animal models, has led to trials for the prevention of diabetes. In addition, aberrant immunologic reactions (eg, insulin autoantibodies after insulin therapy, Graves' disease after monoclonal anti-T-cell therapy in multiple sclerosis) can complicate standard and experimental therapies. We therefore believe that an understanding of the immunogenetics and immunopathogenesis of endocrine disorders can aid in the prevention of morbidity and mortality for these related diseases. (*J Allergy Clin Immunol* 2003;111:S624-36.)

Key words: Type 1 diabetes, HLA, autoantibodies, Addison's disease, APS-1, APS-2, XPID syndrome, Graves' disease, polyendocrine autoimmunity, premature ovarian failure

An increasing series of endocrine disorders are now recognized to be immune mediated. Immunologic therapies can induce immune-mediated endocrine disorders, and standard therapies of endocrine diseases can be complicated by deleterious immunologic responses. The presence of autoimmune disorders in an individual serves as a "bioassay" that the individual and their family are at increased risk for other autoimmune diseases whose early diagnosis can prevent morbidity and even death.

We will review immunologic endocrine disorders with an emphasis on areas in which a knowledge of immuno-

Abbreviations used

AAD:	Autoimmune Addison disease
ACTH:	Adrenocorticotrophic hormone
ADA:	American Diabetes Association
AIRE:	Autoimmune regulator
APS-1:	Autoimmune polyendocrine syndrome type 1
BABY DIAB:	Baby Diabetes Study
BB:	Biobreeding
cAMP:	Cyclic adenosine monophosphate
CTLA:	Cytotoxic T-lymphocyte-associated antigen
DAISY:	Diabetes Autoimmunity Study in the Young
GAD:	Glutamic acid decarboxylase
HT:	Hashimoto thyroiditis
IA-2:	Islet associated antigen (ICA512)
IDDM:	Insulin-dependent diabetes mellitus
IH:	Idiopathic hypoparathyroidism
IL:	Interleukin
MHC:	Major histocompatibility complex
MIC-A:	MHC class I-related molecule A
NOD:	Nonobese diabetic
POEMS:	Polyneuropathy, organomegaly, endocrinopathy, serum monoclonal protein, and skin changes
POF:	Premature ovarian failure
PTH:	Parathyroid hormone
TG:	Thyroglobulin
TGA:	Transglutaminase
TPO:	Thyroid peroxidase
TSAb:	Thyroid-stimulating antibody
TSH:	Thyroid-stimulating hormone
TSHR:	Thyroid-stimulating hormone receptor
VNTR:	Variable number of tandem nucleotide repeats
XLAAD:	X-linked autoimmunity-allergic dysregulation syndrome
XPID:	X-linked polyendocrinopathy, immune dysfunction, and diarrhea

logic pathogenesis or immunotherapies influences standard and experimental clinical care.

DIABETES MELLITUS Background

As the knowledge of the pathogenesis of type 1 diabetes increases, periodic updates of diagnostic criteria follow. The American Diabetes Association (ADA) expert committee published new diagnostic criteria according to the causes of diabetes.¹ The terms juvenile onset and insulin-dependent diabetes mellitus (IDDM) are no longer used. The ADA committee recommended using the term type 1A diabetes for immune-mediated diabetes, with its destruction of the islet β cells of the pancreas. Non-immune-mediated diabetes with severe insulin deficiency is termed type 1B.

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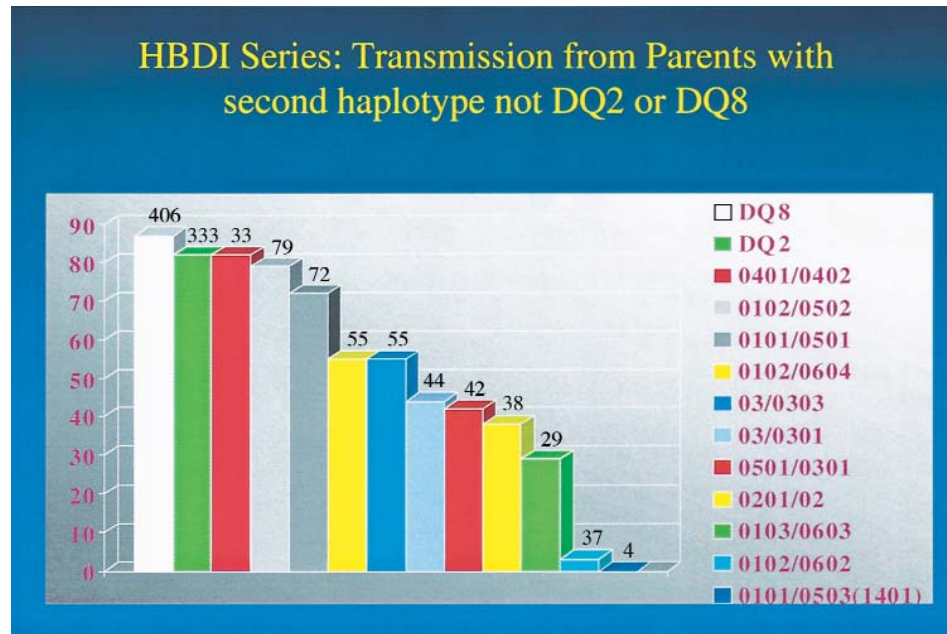


FIG 1. HBDI (Human Biologic Disease Interchange) Series: Transmission from parents with second haplotype not DQ2 or DQ8.

Type 1A diabetes is one of the most common chronic childhood illnesses, affecting in the United States more than 11,000 new cases annually and 2 to 3 per 1000 children by the age of 20 years. More than 90% of white children with diabetes have this disorder, but perhaps as many as 50% of Hispanic and black children with diabetes have none of the hallmarks of type 1A diabetes (eg, no anti-islet autoantibodies or high-risk HLA alleles). As many adults as children have type 1A diabetes. The great majority of adults with diabetes have type 2 diabetes, because the incidence of type 2 diabetes increases dramatically with age. Adults examined clinically with type 2 diabetes (formerly termed non-insulin-dependent diabetes) but expressing anti-islet autoantibodies (approximately 5% to 20%) have accelerated loss of insulin secretion and what has been termed latent autoimmune diabetes of adults. At present, the development of type 1A diabetes is a life sentence to an extremely tedious and only partly effective therapy.

Genetic susceptibility

The concordance for type 1A diabetes is approximately 50% for monozygotic twins, and the risk to a first-degree relative is approximately 5%. The major genetic determinants of diabetes are within the major histocompatibility complex (termed IDDM1), with polymorphisms of multiple genetic loci contributing to risk (Table I).² More than 90% of patients with type 1A diabetes have either DR3,DQ2 (DQ2 = DQA1*0501, DQB1*0201) or DR4,DQ8 (DQ8 = DQA1*0301, DQB1*0302) haplotypes, whereas approximately 40% to 50% of most white populations have one or the other of these haplotypes. More dramatic, between 30% and 50% of patients with

type 1A diabetes are heterozygotes with DR3,DQ2/DR4,DQ8 compared with 2.4% of the general population. The presence of DR3/DR4 heterozygotes is highest in children with diabetes before age 5 (50%) and lowest in adults with type 1A diabetes (<30%). Specific DR and DQ alleles in an autosomal dominant manner can protect from type 1A diabetes. The most common protective molecule, DQA1*0102, DQB1*0602, is present in approximately 20% of control populations versus less than 1% of children with type 1A diabetes.³ Though individuals can have autoantibody positive type 1A diabetes with DQB1*0602, the probability is low enough that rare forms of diabetes should be considered in patients with this allele. The alleles DQA1*0201 with DQB1*0303 (on a DR7 haplotype), as well as DRB1*1401, provide similar protection but are much less frequent compared with DQA1*0102,DQB1*0602. As shown in Figure 1, analysis of transmission of haplotypes from parents to diabetic child show wide variation from highly susceptible with high transmission to protective alleles.

Type 1A diabetes is a heterogenous and/or polygenic disorder, with multiple (approximately 20) non-HLA loci described.⁴ Only one non-HLA gene has been identified with certainty. IDDM 2 on chromosome 11p5.5 contributes approximately 10% of the familial aggregation of type 1A diabetes.⁵ This locus is a polymorphic region that maps to a variable number of tandem nucleotide repeats (VNTR) 5' of the insulin gene.⁶ The long form of the VNTR (≥ 100 repeats, class III) is associated with protection from diabetes. The modest influence of the insulin gene locus may relate to variation in expression of insulin within the thymus. The protective VNTRs are associated with greater messenger RNA expression with-

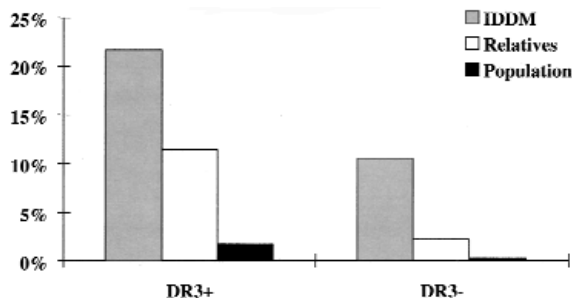


FIG 2. Prevalence of transglutaminase autoantibodies by HLA-DR among patients with type 1 diabetes mellitus, relatives of patients with diabetes mellitus, and general population. (Teaching slides, Type 1 Diabetes: Cellular, molecular and clinical immunology. Eisenbarth GS, editor. www.barbaradaviscenter.org).

in the thymus.⁷ Another locus associated with type 1A diabetes in some populations is IDDM 12 on chromosome 2q33 with polymorphisms of the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).⁸ It is currently unknown how many of the currently reported loci are “false-positives” related to the difficulty of defining genes contributing to complex disorders.

Diabetes-associated autoimmune disorders

Celiac disease. Approximately 1 in 10 patients (11.6%) with type 1A diabetes expressed transglutaminase (TGA) IgA autoantibodies, and more than one half of these individuals are found to have celiac disease on intestinal biopsy (eg, m/z 21 of 30).^{9,10} The antiendomysial autoantibody assay (indirect immunofluorescent assay) is essentially a less sensitive assay for TGA autoantibodies. There is also a high prevalence of TGA autoantibodies in first-degree relatives of patients with type 1 diabetes that are not directly associated with expression of islet autoantibodies.¹¹ A positive biopsy is associated with high levels of TGA autoantibodies (eg, index of >0.5 with 99th percentile of normal an index of approximately 0.05). We recommend obtaining an intestinal biopsy specimen close to the time of positive antibody determination because autoantibody levels can fluctuate markedly, given the short half-life of IgA antibodies. The DR3,DQ2 haplotype is a strong risk factor for celiac disease, and approximated 20% of DR3,DQ2 type 1 patients and one third of DR3,DQ2 homozygous patients with type 1A diabetes express TGA autoantibodies⁹ (Fig 2). The great majority of the patients found to have celiac disease on biopsy after screening for TGA (or antiendomysial) autoantibodies have “asymptomatic” celiac disease, despite marked lymphocytic infiltrates and flattened villae on intestinal biopsy. The treatment of such “asymptomatic” patients varies by physician, in that clinical trials of gluten avoidance have not demonstrated prevention of, for instance, GI malignancy, as has been

demonstrated for symptomatic disease. At the Barbara Davis Center for Childhood Diabetes, TGA autoantibodies are routinely determined annually; biopsy is recommended for type 1 patients with elevated titers of the autoantibody, and a gluten-free diet prescribed for those with positive biopsies. This recommendation is based on the known risks of symptomatic celiac disease (eg, osteoporosis, anemia, gastrointestinal malignancy) with the rationale that intestinal pathology is reversible with gluten avoidance.

Addison's disease. Addison's disease occurs in approximately 1 in 10,000 individuals in the United States. Approximately 1 in 50 patients with type 1 diabetes have 21-hydroxylase autoantibodies, and approximately one fourth of these individuals progress to overt Addison's disease. Despite the availability of replacement steroid therapy, it is not uncommon for patients with Addison's disease to have hypoadrenalism for years before diagnosis¹² or even to die in adrenal crisis, and we therefore currently screen patients with type 1A diabetes for 21-hydroxylase autoantibodies. If 21-hydroxylase autoantibodies are found, annual metabolic evaluation of ACTH and cortisol (cortrosyn stimulation test) are performed to detect early adrenal failure.

Thyroid disease. The Belgian Diabetes Registry found the prevalence of thyroid peroxidase to be 22% in patients with type 1 diabetes.¹³ Thyroid autoantibodies are very prevalent and may be present for years without progression to overt thyroid disease. Thus annual measurement of thyroid stimulating levels (TSH) levels is recommended for cost-effective screening of patients with type 1 diabetes.¹⁴ Alternatively, some endocrinologists determine thyroid autoantibodies and measure TSH only in those with autoantibodies.

Pernicious anemia. The Belgian Diabetes Registry found the prevalence of parietal cell autoantibodies to be 18% in patients with type 1 diabetes. Decreased gastric acid secretion may occur in type 1 diabetes as the result of autoimmune gastric atrophy or Pernicious Anemia.

Vitiligo. The association of vitiligo and type 1 diabetes has been reported, as vitiligo is associated with a series of autoimmune diseases.¹⁵

Insulin allergy and insulin resistance. Essentially, everyone treated with subcutaneous insulin (including human insulin) produces anti-insulin autoantibodies, with a subset of patients having allergic reactions to insulin. Extremely high levels of such antibodies (>0.2 micromolar or 30,000 microunits/mL of maximum insulin binding capacity [insulin circulates at approximately 5 to 500 microunits/mL]) are associated with insulin resistance requiring therapy with >200 Units of insulin/d. With current human insulin and insulin analogues, hypersensitivity reactions to insulin are uncommon. In a patient with insulin hypersensitivity, changing the preparation of insulin (eg, genetically modified human insulin), insulin complexed with zinc versus neutral protein Hagedorn and insulin desensitization often alleviate the problem. Small amounts of dexamethasone (for localized reactions) given with the injection or antihistamines can also be useful.

Environmental factors

Despite decades of searching for environmental factors that trigger type 1 diabetes, only congenital rubella infection has been conclusively associated with the disease. Patients with congenital rubella are at risk for a series of autoimmune illnesses and, in particular, thyroiditis and type 1 diabetes. The Diabetes Autoimmunity Study of the Young (DAISY), following newborn infants from birth, has found no evidence that bovine milk ingestion, enteroviral infection, or vaccination contribute to diabetes risk, but there are conflicting reports relative to the first two environmental factors.¹⁶ In particular, studies from Finland have implicated cow milk ingestion, enteroviruses, and vitamin D consumption in disease risk.¹⁷⁻¹⁹ There are a number of case reports of individuals having anti-islet autoantibodies and then type 1 diabetes (as well as other autoimmune endocrine disorders) after treatment with interferon- α .²⁰ In animal models, drugs such as poly-IC that induce interferon- α can generate insulinitis and diabetes, strengthening the link between induction of diabetes and interferon- α .²¹

Pathogenesis

Humoral autoimmunity. The presence of insulin, GAD, and IA-2 autoantibodies facilitates the diagnosis and prediction of type 1A diabetes, and they are used to identify patients for intervention trials. With the use of radioassays for these three autoantibodies, more than 90% of prediabetic or recent-onset type 1A patients express one or more autoantibodies with assays set to define positivity at ≥ 99 th percentile of normal controls. Assays for autoantibodies reacting with the defined autoantigens are readily standardized, whereas the cytoplasmic ICA assay (indirect immunofluorescence on sections of human pancreas) has proven difficult to standardize and is often reserved for research. As many as 30% of younger "type 2" patients with diabetes have an autoimmune process (express anti-islet autoantibodies), and these patients within 3 years usually progress to requiring insulin.

T cells and inflammatory markers. Detailed studies of the role of autoimmunity in diabetes rely primarily on the availability of animal models, such as the Bio Breeding (BB) rat and the nonobese diabetic (NOD) mouse. There is considerable direct evidence that T cells mediate β -cell destruction in these animal models. The initial indication that lymphocytes and T cells were involved in human β cell destruction was provided by an examination of the pancreas from newly diagnosed diabetic subjects who had insulinitis²² and, in particular, invasion of islets by CD 8⁺ T cells. Sutherland et al observed that within months of the transplantation of a portion of the pancreas from a nondiabetic monozygotic twin into their diabetic twin, insulinitis in the initially normal pancreas developed and diabetes recurred. Mononuclear cell infiltration into the pancreatic islets (insulinitis) and a reduction of insulin producing β cells are key pathologic features of the pancreas when obtained at autopsy from patients with type 1 dia-

TABLE I. Susceptibility loci for type 1 diabetes

HLA-DR	DQA1	DQB1	DRB1	Susceptibility
DR2	0102	0602	1501	Protective
DR2	0102	0502	1601	Predisposing
DR2	0103	0601	1502	Neutral
DR3	0501	0201	0301	Predisposing
DR4	0301	0302	0401	Predisposing
DR4	0301	0302	0401	Predisposing
DR4	0301	0302	0402	Predisposing
DR4	0301	0302	0403	Neutral
DR4	0301	0302	0404	Neutral
DR4	0301	0302	0405	Neutral
DR4	0301	0301	0401	Neutral
DR4	0301	0301	0403	Neutral
DR7	0201	0303	0701	Positive
DR6	0101	0503	1401	Protective

Reviewed in Pugliese A, Eisenbarth GS. Type I diabetes mellitus of man: Genetic susceptibility and resistance. In: Eisenbarth GS, editor. Type 1 diabetes: Cellular, molecular and clinical immunology. www.barbaradaviscen-ter.org. 2002.

betes. A recent case report demonstrated the development of type 1 diabetes in a patient with X-linked agammaglobulinemia, implying that autoantibodies are not required for either the initiation or the progression to type 1 diabetes.²³

The isolation of islet-specific T-cell clones from peripheral blood of human subjects is a challenging undertaking. Investigators have assessed T-cell reactivity to β -cell products by proliferation assays, but international workshops suggest that most such assays cannot distinguish patients with diabetes from control patients. In animal models, multiple anti-islet T-cell clones, both CD4⁺ and CD8⁺, are able to transfer diabetes to immunodeficient recipients. These T-cell clones react with multiple different antigens, including insulin and GAD. Insulin peptide B:9-23, when administered to normal Balb/C mice, can induce insulin autoantibodies and insulinitis²¹ and diabetes in susceptible strains.

Examination of the islets of Langerhans during insulinitis suggests that Fas-mediated apoptosis may provide one mechanism of B-cell destruction. The interaction between Fas on B cells and Fas ligand on infiltrating cells might trigger selective apoptotic islet β -cell death in inflamed islets.²⁴ Cytokines are also likely to play an important role in β -cell destruction.²⁵

Diagnosis and prediction

There are a number of situations in which determination of autoantibodies may be clinically relevant, including where the diagnosis of type 1A diabetes is unclear (children with transient hyperglycemia, black or Hispanic American children with diabetes, and adults with what appears to be type 2 diabetes). Most children with transient hyperglycemia will remain normal, but a subset will have type 1A diabetes. If GAD, insulin, or IA-2 (ICA512) autoantibodies are present in a child with suspected transient hyperglycemia, that child will almost

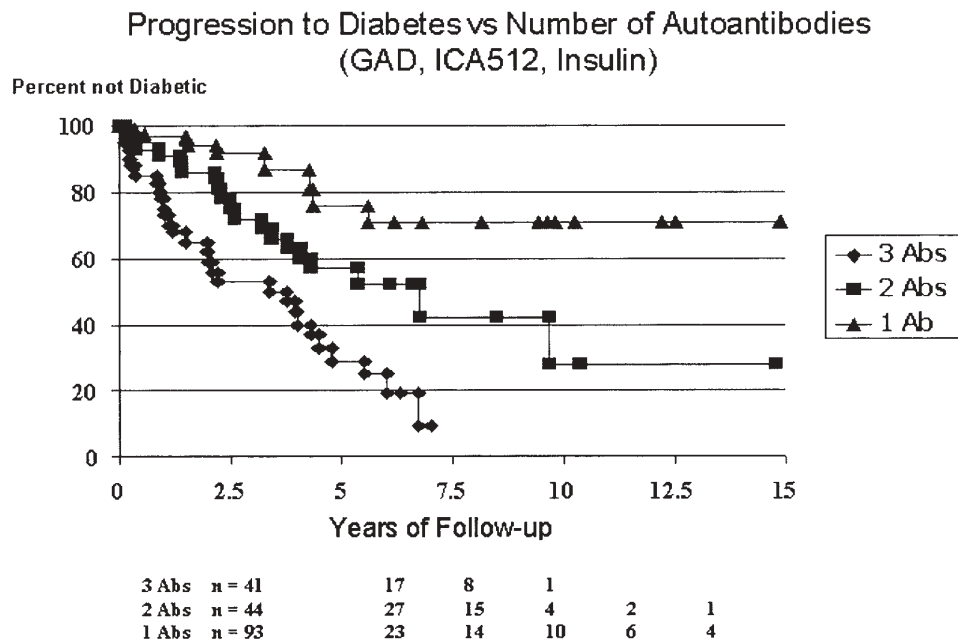


FIG 3. Progression to diabetes versus number of autoantibodies (GAD, ICA512 [IA-2], Insulin). Copyright © 1996, American Diabetes Association. From Diabetes, Vol 45. 1996. p. 926-33. Reprinted with permission from The American Diabetes Association.

TABLE II. Examples of immunologically related interventions preventing type 1 diabetes in animal models

Strategy	Specificity	Animal	Conclusion
Immune suppression	None	NOD and BB	Nonspecific suppression of cell-mediated immunity prevents type 1 diabetes, but long-term immunosuppression is unacceptable.
Anti-CD4	CD4 ⁺ T cells	NOD	Anti-CD4 monoclonals prevent diabetes.
Anti-CD3	CD3 ⁺ T cells	NOD	Anti-CD3 monoclonals reverse diabetes at onset with long duration of effect.
Transplantation	None	NOD and BB	Grafts of marrow, dendritic cells, fetal liver, and thymus protect.
Immune stimulation	None	NOD	Immune activation by agents such as BCG protect.
Immunologic vaccination	Insulin/GAD/HSP60	NOD	Multiple mechanisms, potential activation T regulatory cells.
Oral tolerance	Insulin	NOD	Immune deviation delays diabetes
Hydrolyzed protein diet	Unknown	NOD	Radical scavenging, nutritional specific (eg, lack peptides) protect
Galactosylceramide	NK cells	NOD	Activation CD1 restricted cells
Cytokines	IL-10, TNF, IL-4	NOD	Complex effect dependent often upon timing of Rx
Gene therapy (eg, insulin <i>IL10</i> gene)	Antigens/cytokines	NOD	Multiple potential targets

NOD, Nonobese diabetic mouse; *BB*, BioBreeding rat; *NK*, natural killer; *IL*, interleukin; *THF*, tumor necrosis factor. Reviewed in Chase HP, Hayward AR, Eisenbarth GS. Clinical trials for the prevention of type 1 diabetes. In: Eisenbarth GS, editor. Type 1 diabetes: Cellular, molecular and clinical immunology. www.barbaradaviscenter.org. 2002.

always progress to type 1A diabetes, and intensive metabolic follow-up is advised.²⁶ Independent of the presence of anti-islet autoantibodies, routine monitoring of glucose is important to prevent severe metabolic decompensation that can occur with many forms of diabetes.

It is now possible to predict the development of type 1A diabetes with reasonable accuracy, and programs have been instituted in several countries to screen large populations. In particular, relatives progressing to diabetes have been studied in detail. Expression of two or more autoantibodies (of GAD65, IA-2, or insulin autoantibodies) has a positive predictive value for type 1 dia-

betes exceeding 90% among relatives of patients with type 1 diabetes (Fig 3). A single autoantibody carries a lower risk of approximately 20%. It appears that the presence of multiple anti-islet autoantibodies will be just as predictive in the general population as it is in relatives. The DAISY study from Denver, Colorado, indicates that anti-islet autoantibodies often appear in the highest-risk children (DR3/4 heterozygotes) as early as 9 months of age, with insulin autoantibodies (similar to the Baby Diabetes [BABY DIAB] study results from Germany) frequently the first autoantibody to develop. Given the presence of anti-islet autoantibodies, a significant percentage

of individuals will be found on their first oral glucose tolerance test to have diabetes. The time to progression to diabetes correlates with loss of first-phase insulin secretion after administration of intravenous glucose.²⁷

Treatment

Insulin remains the essential therapy for type 1 diabetes. Several recently introduced human insulin analogues decrease the variability of insulin absorption (eg, rapid acting or long acting) and have improved therapy.²⁸ Devices with either a subcutaneous glucose sensor²⁹ or the use of an electric current to bring glucose through the skin by iontophoreses³⁰ are being used to monitor glucose for 12 to 72 hours. Despite such advances, once most β cells have been destroyed, diabetes management is difficult, and there are multiple acute and chronic complications.

In animal models, nontraditional vaccines (eg, insulin or GAD peptides) that modify a potentially autoreactive and destructive immune response can prevent or delay diabetes (Table II). In NOD mice, insulin injections can prevent diabetes. However, the recent Diabetes Prevention Trial found that there was no impact of low-dose parenteral insulin therapy in delaying the onset of diabetes. Cyclosporine, when given at the onset of diabetes, preserves C-peptide secretion (a measure of remaining islet β cells) and improves metabolic control.³¹⁻³⁴ If administered after diabetes onset, cyclosporine does not prevent deterioration of glucose metabolism. Balancing the risks of cyclosporine therapy versus modest benefit cyclosporine is not used to prevent islet β cell destruction. Trials of other immunomodulatory or immunosuppressive drugs are underway or planned. Pancreas transplantation and recently islet transplantation are important considerations for selected patients with type 1 diabetes and severe complications such as recurrent intractable hypoglycemia. Both can result in "immediate" reversal of hyperglycemia and prevent life-threatening hypoglycemia. Long-term follow-up of islet transplants is lacking, but recent results with the Edmonton protocol indicate that with immunosuppression, significant islet function can be achieved for 1 year in more than 85% of patients.³⁵ In that both pancreas and islet transplants required immunosuppression, such therapy should at present be reserved for those requiring immunosuppression (eg, kidney transplantation) or patients with life-threatening metabolic instability.

INSULIN AUTOIMMUNE SYNDROME

The insulin autoimmune syndrome results from autoantibodies reacting with insulin and can be subdivided by whether the autoantibodies are monoclonal or polyclonal. Patients usually have recurrent hypoglycemia. A monoclonal response is associated with B-lymphocyte tumors. The polyclonal disorder is strongly associated with DRB1*0406 and usually follows therapy with sulfhydryl-containing medications such as methimazole (eg, for treatment of Graves disease).³⁶

TABLE III. Immunogenetic associations with autoimmune thyroiditis

Race	Genotype
British (white)	DQB1*0201, DRB1*0201
North American (white)	DR5
German	DR3, DQB1*0201,DQB1*0301
Japanese	A2, DRB4*0101
Turkish	DQA1*0301

AUTOIMMUNE THYROID DISEASE

Graves' disease

Background. Robert Graves first discovered the association of goiter, palpitations, and exophthalmos in 1835. Graves' disease is defined as a form of hyperthyroidism associated with a diffuse hyperplastic goiter, resulting from the stimulation of the TSH receptor (TSHR) by a TSHR autoantibody, known as thyroid-stimulating antibody (TSAb). It is clear now that the TSAb bind to and activate the TSH receptor on thyroid cells. Graves' disease can present either as an isolated disorder or as an overlap disorder with thyroiditis (discussed below). Graves' disease also affects the eyes (Graves' ophthalmopathy) and the skin (localized dermatopathy or myxedema), but the causes of these components of the disease are not known.

Pathogenesis and genetics. Graves' disease, like thyroiditis, appears to occur in genetically susceptible individuals, with a female preponderance. The rate of concordance for Graves' disease is approximately 20% among monozygotic twins and is much lower among dizygotic twins. In whites, HLA-DR3 and HLA DQA1*0501 are associated with Graves' disease, whereas HLA DRB1*0701 is protective.^{37,38} Graves' disease is also associated with polymorphism of the CTLA-4 gene in several racial groups. Linkage analysis of candidate genes has identified loci on chromosomes 14q31, 20q11.2, and Xq21 that are associated with susceptibility to Graves' disease.³⁹⁻⁴¹

Patients with Graves' disease have diffuse lymphocytic infiltration of the thyroid gland and sensitization to a number of thyroid antigens, particularly thyroid peroxidase, TSHR, thyroglobulin, and the sodium-iodide cotransporter in thyroid tissue.⁴² These autoantibodies include TSAb, thyroid-inhibitory antibodies, and thyroid-stimulating-blocking antibodies. Clinical hyperthyroidism develops if TSAb predominates in the circulation. Interestingly, over the last decade there has emerged another recognizable immunologic phenomena of fluctuating hypothyroidism and hyperthyroidism (Thyroid Yo-Yo), which underlies the importance of periodic thyroid function testing in hypothyroid patients taking thyroid hormone replacement.⁴³ TSAb is measured by the capacity of serum immunoglobulin to stimulate cAMP production in cultured human thyroid cells, whereas inhibitory (blocking)

antibody is measured by the degree of inhibition of TSH stimulation of cAMP production in cultured human thyroid cells by serum immunoglobulins. Determination of TSAb is used for the prediction of neonatal thyrotoxicosis.

Other endocrine diseases have similar antibody-mediated pathophysiology. Flier et al⁴⁴ described a group of antibodies that blocked the action of insulin by binding to insulin receptors, causing insulin resistance. This is similar to the situation in hypothyroidism, whereby TSH-inhibitory antibodies may lead to the resistance of TSH action and therefore to an increase in TSH levels. Insulin receptor antibodies that stimulate rather than block the insulin receptor have also been described.⁴⁴ It is unclear how a patient's autoantibodies can have a dual function. Only cross-linked antibody Fab fragments stimulate the insulin receptor, whereas monomeric Fab fragments universally block.⁴⁴

The production of TSAb depends on T lymphocytes and T cells that recognize multiple epitopes of the TSHR.⁴⁵ Although TSAb cause Graves' hyperthyroidism, the serum antibody concentration can be low or even undetectable in a few patients. This may be due to assay insensitivity, misdiagnosis, or intrathyroidal production of antibodies.⁴² Drugs may precipitate hyperthyroidism. For example, hyperthyroidism developed in one third of patients with multiple sclerosis treated with Campath 1-H⁴⁶ (anti-CD 52 monoclonal antibody).

The association between Graves' hyperthyroidism and Graves' ophthalmopathy suggests that the two disorders result from an autoimmune response to one or more antigens located in the thyroid and orbit, respectively. TSHR can be expressed by a preadipocyte subpopulation of orbital fibroblasts,⁴⁷ and IL-4 and IL-10 are produced in response to T cells in an animal model of ophthalmopathy.⁴⁸ It is possible that a form of the TSHR or a similar protein is expressed in the orbit and may serve as a cross-reactive target for the TSAb.⁴⁸ Smoking is a strong risk factor for the development of Graves' ophthalmopathy.⁴⁹ Approximately 1% of patients with Graves' disease will have myasthenia gravis, indicating that autoimmunity to multiple organs may coexist in these patients.⁴⁹

Diagnosis and prediction. More than 50% of patients with hyperthyroid Graves' disease relapse after a 12-month course of antithyroid drugs, the actual percentage varying among populations and with their iodine intake. The measurement of TSHR autoantibodies by competitive radioreceptor assay or by thyroid cell bioassay in patients with Graves' disease can be a useful predictor of relapse and remission.⁵⁰

The validity of predicting neonatal Graves' disease by using the measurement of biologically active TSHR antibodies in the mother has been well documented. High titers in the third trimester is a good predictor of neonatal hyperthyroidism or with blocking antibodies, of hypothyroidism.⁵¹ Pregnancy is a time when thyroid autoantibodies generally decrease in titer as the result of secretion of trophoblast factors, which are immunosuppressive, whereas postpartum thyroid autoimmunity is common.

The diagnosis of Graves' hyperthyroidism is usually

based on the clinical and biochemical manifestations of hyperthyroidism. With current sensitive TSH assays, both hyperfunction (low TSH) and hypofunction (high TSH) of the thyroid can be diagnosed. In that a high serum thyroxine can result from Graves' disease or glandular destruction with thyroiditis, the presence of TSAb aids diagnosis, as does estimation of radioactive iodine thyroid uptake (only tested in nonpregnant, non-breast-feeding patients). Free thyroxine measurements can aid in diagnosis for states with increased thyroid binding molecules (eg, estrogen therapy).

Treatment. Current treatments for Graves' hyperthyroidism consist of antithyroid drugs, radioactive iodine, and surgery. Antithyroid drugs are effective, but relapses often occur upon discontinuation of therapy. Different treatment regimens exist; the main methods are the block and replacement regimen and the reducing regimen, but there are no major differences in clinical outcomes between them.⁵² In the United States, for adults, radioactive iodine administration is the favored therapy. Ablation of the thyroid gland is effective, but often at the expense of iatrogenic hypothyroidism. The treatment of Graves' ophthalmopathy remains unsatisfactory. The usage of corticosteroids provides some benefit, but other immunosuppressive agents seem to be less efficacious.

Thyroiditis

Background. Thyroiditis is one of the most common autoimmune disorders of the endocrine system. Chronic progressive autoimmune thyroiditis, known as Hashimoto thyroiditis (HT), predominantly affects middle-aged women. This form of thyroiditis should be differentiated from transient thyroiditis syndromes associated with postpartum disease, de Quervain thyroiditis, or other rare thyroiditis disorders, and the presence of high-titer antithyroid antibodies and clinical presentation (eg, pyogenic thyroiditis characterized by thyroid pain and fever) usually suffice for diagnosis and should have biopsy to define the organism. These disorders tend to result in transient hypothyroidism but do not generally lead to chronic thyroid dysfunction.⁵³ HT is characterized by a dense thyroidal accumulation of lymphocytes, plasma cells, and occasional multinucleated giant cells. The epithelial cells are enlarged, with a distinctive eosinophilic cytoplasm, owing to increased number of mitochondria (Hurthle cells).

Pathogenesis. Thyroiditis appears to occur in genetically susceptible populations, but the lack of consistency of HLA associations is unusual (Table III), whereas, for example, HLA associations with type 1A diabetes are consistent for HLA, DR, and DQ haplotypes in multiple populations.⁵⁴ A number of viruses have been postulated to induce autoimmunity in the thyroid, such as the human T-cell lymphotropic virus type 1.⁵⁵

T cells play a critical role in the development of HT, interacting with thyroid follicular cells and extracellular matrix. T cells may destroy thyroid tissue by direct cytotoxicity or indirectly by cytokine secretion. T-cell clones, capable of killing thyroid follicular cells in an HLA class

I-restricted fashion, have been isolated from different patients with HT. Cytokines, including IL-1 β , IL-6, IL-2, IL-8, and IL-10, are produced during thyroiditis.⁵¹ Adhesion molecules, such as intercellular adhesion molecule type 1, hermes-1, lymphocyte function-associated molecule 3, and neural cell adhesion molecule may play a central role.

Most patients with autoimmune hypothyroidism caused by HT have serum antibodies to thyroglobulin (TG) and thyroid peroxidase (TPO) and occasionally to the TSHR (Table IV). Although TG antibodies are found mainly in patients with autoimmune thyroid disease, they are also detected in normal individuals or after viral infections. It appears that thyroglobulin antibody positivity alone is not sufficient to cause thyroid dysfunction, but a role for these autoantibodies in the perpetuation of the disease cannot be ruled out. Thyroid peroxidase is a major autoantigen, and autoantibodies to TPO are closely associated with disease activity. It is not clear whether immune responses to these autoantigens initiate thyroiditis or if they are secondary to thyroid destruction. A newly recognized autoantigen is the sodium/iodine symporter, the thyroid-specific protein responsible for the uptake of iodine.⁵⁶

Diagnosis and treatment. The diagnosis and treatment of chronic thyroiditis has changed very little over the past decade. The addition of tri-iodothyronine to thyroxine replacement therapy has recently been suggested to improve neurobehavioral symptoms of hypothyroidism.⁵⁷ Fine needle aspiration of the thyroid is used to rule out thyroid cancer, particularly in patients with a suspicious goiter. Hypothyroid patients taking thyroxine replacement therapy who may wish to start estrogen therapy should have their thyroid function tested more regularly, because estrogen alters thyroid-binding globulin physiology.⁵⁸ Continuous monitoring of thyroid function is essential to avoid overreplacement, because this may result in premature osteoporosis and cardiac arrhythmias.

ADDISON'S DISEASE

Background

In 1849, Thomas Addison described a group of patients who died of severe anemia with diseased adrenal glands. Addison's disease is a chronic disorder of the adrenal cortex, characterized by deficient production of adrenocortical hormones together with increased secretion of pituitary adrenocorticotrophic hormone (ACTH). Pathologic examination of the adrenal glands in autoimmune Addison's disease reveals fibrosis with a mononuclear cell infiltrate, occasional plasma cells, and rare germinal centers.⁵⁹ In developed countries, the most common cause of primary adrenal failure is autoimmunity (75% to 80% of the cases of adrenal insufficiency), whereas tuberculosis is the second most frequent cause. Approximately 50% to 60% of patients with autoimmune Addison's disease (AAD) have during their lifetime other autoimmune disorders. AAD can present in three main clinical forms: autoimmune polyendocrine syndrome type 1 (APS-1), autoimmune polyendocrine syndrome type 2 (APS-2), and as an isolated disease. Type 1 diabetes develops in approximately 10% of

patients with Addison's disease. A patient with type 1 diabetes who subsequently has Addison's disease usually has a falling insulin requirement and frequent hypoglycemic reactions. Hyperpigmentation can be absent, despite severe adrenal insufficiency, causing hypoglycemia.

Pathogenesis and genetics

The presence of antibodies to the adrenal cortex enzyme 21-hydroxylase is characteristic of Addison's disease. The presence of autoantibodies against 21-hydroxylase can be found in more than 90% of recent onset patients. Although the role of these autoantibodies in the pathogenesis of AAD is unclear, their detection is clinically useful because they have a high diagnostic accuracy. False-positive 21 hydroxylase antibodies have been reported in some adrenal tumors, infections⁶⁰ such as tuberculosis, and adrenoleukodystrophy (disorder of fatty acid metabolism with central nervous system disease and adrenal destruction); but in general, such patients with current assays are negative.⁶¹ Unlike Addison's disease, adrenoleukodystrophy can be identified in a young male patient with adrenal insufficiency, negative for 21-hydroxylase antibodies, with progressive spastic paraparesis and raised urinary concentrations of C22-26 fatty acids.

With regard to the MHC-linked genes, there is a general consensus for AAD that the major association is with HLA B8 and DR3, even when patients with AAD are analyzed separately from those who have other autoimmune disorders. A recent study showed a significant increase in frequency of transmission of the HLA-DR4 haplotype (DRB1*0404,DQ8) from parents to children affected with AAD (irrespective of presence or absence of associated type 1 diabetes or anti-islet antibodies) but not to unaffected children.⁶² The highest-risk genotype for Addison's disease is similar to type 1A diabetes with DR3/4, DQ2/DQ8 for both Norway and the United States. Addison's disease develops in approximately 1 in 10,000 individuals in the United States, but those with DR3,DQ2/ DR4,DQ8 have a risk as high as 1:500 to 1:200,⁶³ with almost one half of patients with Addison's disease in the United States having this genotype compared with 2.4% of the general population. In addition, an atypical HLA molecule MIC-A (MHC class I-related) is also associated with Addison's disease.⁶⁴

Diagnosis and treatment

In symptomatic patients, AAD is diagnosed by the failure of serum cortisol to rise after an ACTH stimulation test in the presence of elevated basal ACTH levels, and usually (>90%) 21-hydroxylase autoantibodies are present. We typically screen patients with type 1 diabetes, hypoparathyroidism, and polyendocrine autoimmune disorders for 21-hydroxylase autoantibodies, and, if present, annually evaluate ACTH and cortisol response to ACTH. All patients with AAD will need life-long oral hydrocortisone and fludrocortisone replacement and life-long evaluation for associated disorders such as thyroid autoimmunity, pernicious anemia, type 1 diabetes, and so forth.

TABLE IV. HLA and autoantigen associations of autoimmune endocrine disorders

Disease	HLA association	Autoantigen
Graves' disease	DR3	TSH receptor
Insulin autoimmune syndrome	DR4, DRB*0406	Insulin
Celiac disease	DR3, DR2, DQ8	Transglutaminase
Type 1A diabetes	DR3/4, DQ 2/8	Insulin, GAD, IA-2
Addison's disease	DR3, DR4	21-Hydroxylase
Thyroiditis, see Table II.		Thyroglobulin, peroxidase.

IDIOPATHIC HYPOPARATHYROIDISM

Background

Idiopathic hypoparathyroidism (IH) results from deficient parathyroid hormone (PTH) secretion without an identifiable cause.⁶⁵ This disease is a common component of APS-1 in infants or young children. It may also occur sporadically in adults, most often in women affected by HT. An autoimmune cause for IH has been suggested because of its association with other autoimmune conditions.⁶⁶

Pathogenesis

Neufeld and colleagues⁶⁵ were the first to report autoantibodies to the parathyroid glands, but subsequent studies revealed that these antibodies often appeared to be directed against mitochondrial antigens. As antimitochondrial antibodies are common in a variety of autoimmune diseases,⁶⁷ the specificity of these antibodies in the context of IH is in doubt. The function of the parathyroid antibodies was more clearly shown by Posillico et al,⁶⁸ whereby they inhibited the secretion of PTH by binding the antibodies to the cell surfaces of human parathyroid cells. Furthermore, autoantibodies in the sera of patients with IH have been reported to be cytotoxic for cultured bovine parathyroid cells by an antibody-mediated cytotoxicity dependent on complement fixation and activation. There is evidence of antibodies to the calcium sensing receptor. As in many other autoimmune conditions, the initiating autoantigen in hypoparathyroidism remains a mystery.

PREMATURE OVARIAN FAILURE

Background

This is a condition of ovarian failure that occurs before or after puberty.⁶⁹ Girls should not be prepubertal by age 13 and should menstruate within 5 years after onset of puberty. Premature ovarian failure is defined as amenorrhea, elevated gonadotropin levels, and hypoestrogenism before age 40 years. The estimated incidence of premature ovarian failure (POF) is approximately 1%. The association of POF with several autoimmune conditions has been established with a reported frequency of 17%.⁷⁰ Two distinct clinical scenarios can be identified with this condition and are described below.

Idiopathic POF with adrenal autoimmunity. Approximately a quarter of women with Addison's disease have amenorrhea in the course of the disease, and 10% have ovarian failure. Steroid cell autoantibodies seen in Addison's disease cross-react with the theca internal/granulosa layers of the ovarian follicles, and its presence is a marker for the association of Addison's disease and ovarian failure. Patients with steroid cell autoantibody-positive Addison's disease without ovarian failure are at high risk of developing ovarian failure, although the latency period can be long.⁷¹ Lymphocytic oophoritis is a consistent finding in patients with steroid cell autoantibody-positive ovarian failure, supporting the autoimmune nature of idiopathic ovarian failure. The expression of MHC class II on granulosa cells of patients with ovarian failure may allow T lymphocytes to potentiate a local autoimmune response.

Idiopathic POF with exclusive manifestations of ovarian autoimmunity. The great majority (90% to 98%) of women with ovarian failure neither have Addison's disease nor steroid cell autoantibodies.⁷⁰ Autoimmunity as the cause of this condition remains controversial, as lymphocytic infiltration is consistently absent. Approximately 14% of these patients have evidence of thyroid autoimmunity. In approximately 10% of patients with isolated ovarian failure without Addison's disease, numerous ovarian follicles remain. These patients are categorized as having a resistant ovary syndrome that is insensitive to ovulation induction with exogenous gonadotrophins.

Treatment

Ovum donation is the treatment of choice for infertility in women with POF. One should be aware that autoimmune ovarian failure is a waxing and waning disease susceptible to spontaneous remissions and occasional conceptions. Screening for other autoimmune endocrinopathies (eg, Addison's disease, thyroid autoimmunity, pernicious anemia) should be considered in patients with idiopathic premature ovarian failure.

LYMPHOCYTIC HYPOPHYSITIS

Background

Lymphocytic hypophysitis is a rare inflammatory lesion of the pituitary gland. A little more than 100 cases have been described since the original report in 1962. This condition is more common in female individuals and affects women during late pregnancy or in the postpartum period. It has a strong association with other autoimmune conditions.^{72,73}

Pathogenesis

The morphologic features of hypophysitis resemble those of other autoimmune endocrinopathies. The absence of granulomata on microscopy distinguishes this condition from the granulomatous hypophysitis seen in association with tuberculosis, syphilis, sarcoidosis, and giant cell granuloma. Antipituitary autoantibodies have been isolated in only a minority of patients with the disease.⁷³⁻⁷⁶

Diagnosis and treatment

Owing to the lack of specificity of any of the markers of the disease, the diagnosis can only be confirmed with histologic examination. The clinical presentation of patients with this disease can result from the mass effect of the enlarged pituitary gland, which can be diagnosed with magnetic resonance imaging. Nearly 40% of patients have hyperprolactinemia, and approximately 65% of patients have anterior hypopituitarism insufficiency.⁷³ Since this condition may be potentially transient, conservative treatment may be sufficient and may also eliminate the need for aggressive pituitary surgery.

AUTOIMMUNE POLYENDOCRINE SYNDROMES

Background

The autoimmune polyendocrine syndromes are a constellation of autoimmune disorders characterized by multiple autoimmune disorders, including endocrine gland failure or hyperactivity (eg, Graves' disease). We have already described above some of the components of the syndromes in more detail. The syndromes include (1) APS-1, (2) APS-2, (3) X-linked polyendocrinopathy immune dysfunction and diarrhea (XPID syndrome), (4) non-organ-specific autoimmunity (eg, lupus erythematosus) associated with anti-insulin receptor antibodies, (5) thymic tumors with associated endocrinopathy, (6) Graves' disease associated with insulin autoimmune syndrome, and (7) polyneuropathy, organomegaly, endocrinopathy, serum monoclonal protein, and skin changes (POEMS). We discuss below APS type 1 and type 2, the XPID, and POEMS syndromes (Table V).

Autoimmune polyendocrine syndrome type 1

Background. The first description of the association between hypoparathyroidism and candidiasis was published in 1929,⁷⁷ and the association of these two diseases with idiopathic adrenal insufficiency was reported in 1946.⁷⁸ APS-1 is a rare disorder. The major components of APS-1 are chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. In the past, to define this syndrome, at least two of these diseases had to be present in one individual.^{65,79} With the identification of mutations of the AIRE (autoimmune regulator) gene, characteristic mutations of the AIRE gene can contribute to early diagnosis. In general, the first manifestation usually occurs in the childhood, and the complete evolution of the three main diseases usually take place in the first 20 years of life. Diseases continue to appear until at least the fifth decade.⁶⁵ The spectrum of associated minor clinical diseases include other autoimmune endocrinopathies, autoimmune or immune-mediated gastrointestinal diseases, chronic active hepatitis, autoimmune skin diseases, ectodermal dystrophy, keratoconjunctivitis, immunologic defects, asplenia, cholelithiasis, and mucosal cancer.

Pathogenesis/genetics. The gene for APS type 1 has been cloned (AIRE), and the mutation R257X was shown to be responsible for 82% of Finnish APS-1 alleles.⁸⁰ DQB1*0602 provides some protection from progression to type 1 diabetes.⁸¹

Treatment. Hormonal substitution remains the mainstay of treatment for the different endocrine failures. Mucocutaneous candidiasis is treated with antifungal drugs such as fluconazole and ketoconazole. Since ketoconazole is a P 450 cytochrome inhibitor, all patients with APS-1 should be monitored closely for any evidence of adrenocortical decompensation. Screening of affected individuals for other new disorders is necessary. Therefore, annual autoantibody (21-hydroxylase, anti-islet, antithyroid), electrolytes, calcium, thyroid hormone, hepatic enzymes, and vitamin B₁₂ measurements are recommended in these patients. Asplenicism develops in a subset of patients. Patients with Howell Jolly body should be evaluated for asplenicism, and, if present, should be treated prophylactically for infection (meningococcal, hemophilus, and pneumococcal vaccination [if no antibody response to pneumococcal immunization, prophylactic daily antibiotics]). Oral candidiasis requires aggressive therapy, because mucosal cancer is thought to be preventable with antifungal therapy (amphotericin lozenge, prompt biopsy of suspicious lesions, elimination of sharp points on teeth, and plastic materials in mouth).

Autoimmune polyendocrine syndrome type 2

Background/genetics. APS-2, also known as Schmidt's syndrome, is the most common of the immunoendocrinopathies. It occurs more frequently in female individuals and is commonly diagnosed between 20 and 40 years of age.⁸² APS-2 is usually defined by the occurrence in the same individual of two or more of the following: AAD, type 1 diabetes, and autoimmune thyroid disease. Other endocrine and nonendocrine disorders are associated with APS-2 (Table V).

Pathogenesis and genetics. Although this condition tends to aggregate in families, there is no discernible pattern of inheritance. Many of the disorders of APS-2 are associated with an HLA-extended haplotype formed by HLA-A1, HLA -B8, MICA-5.1, HLA DR3,DQA1*0501,DQB1*0201. Recently, Yu et al highlighted the association of DRB1*0404 with the haplotype DQ2/DQ8, which is likely to account for a significant portion of the association between Addison's disease and type 1 diabetes mellitus.⁶² The MICA-5.1 allele is strongly associated with Addison's disease.⁶⁴ A number of studies have reported an association of cytotoxic T lymphocyte antigen-4(CTLA) gene polymorphism with APS-2 component disorders.⁸³⁻⁸⁵

Treatment. The treatment of APS-2 includes early diagnosis of associated disorders and long-term follow-up. Patients with suspected Addison's disease and hypothyroidism should be evaluated and treated for adrenal insufficiency before replacement of thyroid hormones to avoid Addisonian crisis. There has been one fascinating case report of a patient with 21-hydroxylase

TABLE V. Comparison of APS-1 and APS-2

Type 1	Type 2
Addison's disease: 60% to 72%	Addison's disease: 70%
Autosomal recessive	Polygenic inheritance
Autoimmune regulator gene (AIRE) (chromosome 21q22.3)	(some disease components associated with DQ2/DQ8)
Equal sex incidence	Female preponderance
Onset in infancy	Peak incidence ages 20 to 60
Mucocutaneous candidiasis	No mucocutaneous candidiasis
Hypoparathyroidism common	Hypoparathyroidism rare
Type 1 diabetes mellitus: Lifetime frequency: 14%	Type 1 diabetes mellitus: approximately 50%

Reviewed in Eisenbarth GS. Autoimmune polyendocrine syndromes. In: Eisenbarth GS, editor. Type 1 diabetes: Cellular, molecular and clinical immunology. www.barbaradaviscenter.org. 2002.

autoantibodies treated for Graves' eye disease with a 6-month course of glucocorticoids. In this patient, 21-hydroxylase autoantibodies became negative and adrenal function was restored to normal. This remission was reported to have lasted for 100 months at last follow-up.⁸⁶

XPID syndrome

The extremely rare XPID syndrome is also termed XLAAD (X-linked autoimmunity-allergic dysregulation syndrome). The gene mutated in XPID is the same gene mutated in Scurfy mice, and the mutation in human beings produces overwhelming neonatal autoimmunity, including type 1A diabetes. For Scurfy mice, bone marrow transplantation is an effective therapy, and there is one report in human beings that bone marrow transplantation will reverse the disease. For both APS-1 and XPID, the mutated genes are transcription factors.

POEMS syndrome

POEMS syndrome is associated with plasmacytomas and osteosclerotic lesions. The etiologic factors of this constellation of diseases are not well defined, but radiation therapy to localized lesions is often of benefit, and there is a report that autologous hematopoietic cell transplantation benefited a patient with refractory disease.⁸⁷

CONCLUSIONS

Immunologic assays and therapies are of increasing importance to a broad spectrum of endocrine disorders. In particular, type 1A diabetes is one of the best-studied organ-specific autoimmune diseases. For diabetes, it is possible to predict disease in human beings and prevent disease in animal models. Thus there is a major effort underway to develop effective preventive therapies in human beings. Similar questions are being asked for many autoimmune disorders, and it is hoped that with improved basic understanding, the family of autoimmune diseases that afflict patients and their families with diabetes will be preventable in the long term and better treated in the short term.

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