Autoimmune Endocrine Disorders

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Key Points

- Type 1 diabetes serves as a model for autoimmune endocrine disorders.
- Autoimmune polyendocrine syndrome type 1 (APS-1) also known as autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED) is an autosomal recessively inherited disorder caused by mutations of the *AIRE* gene resulting in multiple autoimmune diseases.
- Autoimmune polyendocrine syndrome type 2 (APS-2) is a common disorder associated with type 1 diabetes, primary adrenal insufficiency, and hypothyroidism.

34.1 Introduction and Background Information

It is hypothesized that autoimmune endocrine diseases progress through a series of stages starting with genetic susceptibility followed by an environmental trigger that initiates the autoimmune process and ultimately culminating in overt clinical disease. Type 1 diabetes serves as a model disorder for autoimmune endocrine disorders. Initial disease schema proposed by Dr. George Eisenbarth [1] has recently been updated to include the possibility of waxing and waning of the disease and persistence of glandular function after onset of disease [2]. The model proposes several progressive stages for the development of type 1 diabetes: genetic predisposition, overt immunological abnormalities, progressive β-cell dysfunction, and overt diabetes (Fig. 34.1).

34.1.1 Genetic Risk

There are multiple genes that have been associated with the risk for autoimmune disease [3]. Genes may influence the risk for the development of autoimmunity and/or the risk for the progression from autoimmunity to glandular dysfunction. Data derived from prospective follow-up of high-risk individuals are beginning to tease out these

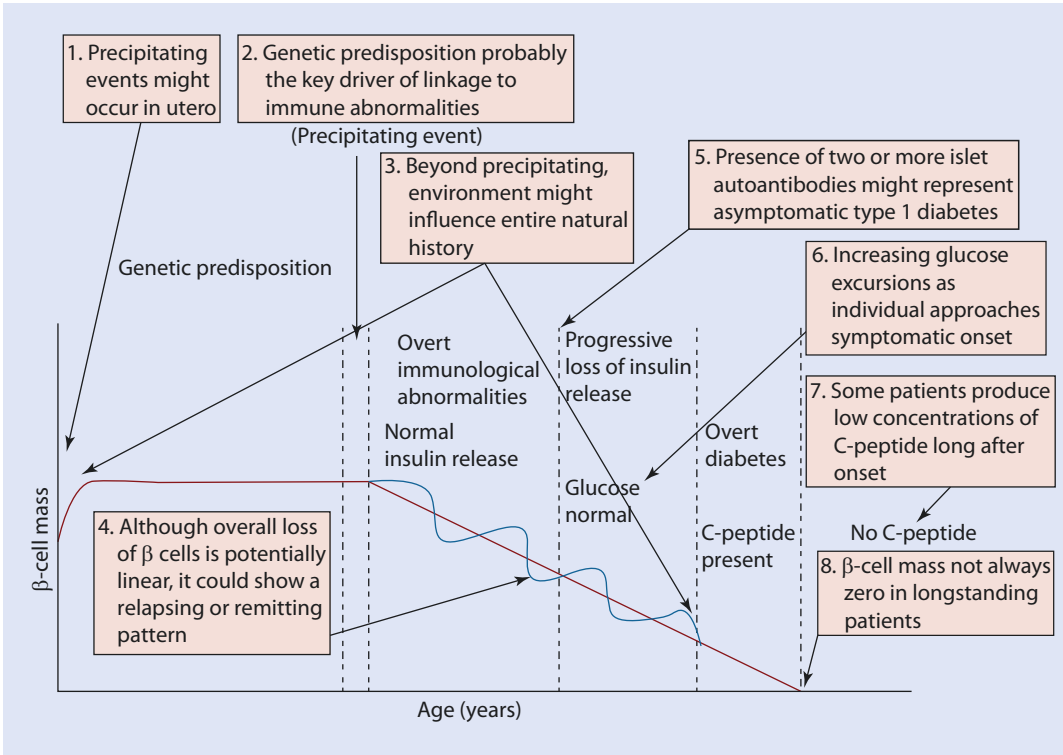

Fig. 34.1 Model for the development of type 1 diabetes. Highlighted are updates in the understanding of the pathophysiology of type 1 diabetes (From Atkinson et al. [2]. Reprinted with permission from Elsevier)

relationships. The most consistent risk has been shown with the genes that make up the human leukocyte antigens (HLA) found on chromosome 6. In subjects followed for type 1 diabetes, HLA alleles have been differentially associated with the first positive diabetes-related autoantibody. HLA DR4-DQ 8 has been associated with insulin autoantibodies as the first antibody, and HLA-DR3-DQ 2 has been associated with GAD autoantibodies. These data suggest that these HLA alleles may be important for the initiation of the autoimmune process. HLA may also influence the progression from autoimmunity to disease. For example, HLA-DRB1*15:01-DQA1*01:02-DQB1*06:02 has been shown to be protective for the progression of autoimmunity from a single positive autoantibody to multiple positive autoantibodies and dysglycemia [4]. It has been shown that subjects that are HLA identical for the DR3/4 locus as their sibling with diabetes have a risk for developing diabetes-related autoimmunity of approximately 75% and diabetes risk of approximately 50% after 5 years of follow-up [5]. Thus, the risk for development of autoimmune disease can be additive.

HLA alleles partially explain the disease associations observed in APS-2. DR3-DQ2 and DR4-DQ8 are associated with autoimmune hypothyroidism.

Genes outside of the HLA region have also been implicated in the risk for autoimmune diseases. Some of these genes increase an individual's likelihood of developing any autoimmune disease, while other genes are associated with specific autoimmune conditions (e.g., the variable number of tandem repeats VNTR of the insulin gene). Specific genes may be associated with progression from autoimmunity to β-cell dysfunction (e.g., PTPN22) [6].

34.1.2 Environmental Factors

Despite the strong genetic influence in development of autoimmune diseases, not all with genetic risk develop disease. Environmental triggers have been hypothesized to be important in the development of autoimmune disease. The classic example of this is celiac disease, where the environmental trigger, gluten, is known. In type 1 diabetes, multiple environmental triggers have been proposed [7]. Environmental triggers may influence both steps of the process: initial development of autoimmunity and progression from autoimmunity glandular dysfunction. Earlier introduction of cereals and gluten (<4 months) has been associated with risk for type 1 diabetes [8, 9] and celiac disease [10]. Increased weight at 12 months has been associated with risk for diabetes-related autoimmunity but not progression from autoimmunity to type 1 diabetes [11]. Emerging data suggests that enteroviral infections may be associated with type 1 diabetes [7, 12]. There may be protective environmental factors such as breast feeding [13]. Other active areas of research include the influence of the intestinal microbiota and development of autoimmunity and disease [14]. It is likely that extensive genetic-genetic and genetic-environmental interactions influence not only the development autoimmunity but also progression of autoimmunity to disease.

34.1.3 Markers of Autoimmunity

While the autoimmune process is thought to be mostly T-cell mediated, the autoimmune process is marked by the presence of autoantibodies (antibodies against self-antigens) (Table 34.1). Diabetes-related autoantibodies include antibodies against insulin (IAA), GAD65, IA-2, and ZnT8. These autoantibodies are used in the research and clinical setting to identify patients at an increased risk for an autoimmune disease and to confirm autoimmunity as the underlying cause of the disease in an affected individual. Autoantibodies can be detected in the serum prior to the development clinical disease. Studies in subjects with diabetes-related autoantibodies show that the risk for the development of diabetes increases with increasing number of diabetes-related autoantibodies [15], the persistence of the autoantibodies on multiple tests [16], and autoantibody level and affinity of autoantibodies for the antigens [17, 18]. Long-term follow-up of subjects at risk for type 1 diabetes suggests that some of those with single autoantibodies can progress to multiple autoantibodies and diabetes [19].

The presence of disease-related autoantibodies can precede the development of overt disease by many years. For example, in patients with type 1 diabetes and antibodies associated with thyroid disease, thyroid disease developed over 10–20 years in 80% of the subjects with positive

Table 34.1 Autoimmune endocrine disorders

Disease	Autoimmune markers	Diagnosis of disease
Type 1 diabetes	Insulin autoantibodies (IAA) GAD65 autoantibodies IA-2 autoantibodies ZnT8 autoantibodies	Glucose Hemoglobin A1c
Hypothyroidism	Thyroid peroxidase Thyroglobulin autoantibodies	TSH Thyroid hormone levels
Hyperthyroidism	Thyroid-stimulating immunoglobulin	TSH Thyroid hormone levels
Adrenal insufficiency	21-Hydroxylase autoantibodies	ACTH Cortisol PRA Electrolytes Dynamic testing with cosyntropin
Gonadal failure	21-Hydroxylase autoantibodies	Primary or secondary amenorrhea Elevated FSH/LH, low estradiol or testosterone
Celiac disease	Tissue transglutaminase autoantibodies	Small intestinal biopsy
Pernicious anemia	Intrinsic factor autoantibodies Parietal cell antibodies	Vitamin B12 deficiency Gastric biopsy

antibodies [20]. Insulin autoantibodies are often the first to develop. Antibodies to IA-1 and ZnT8 are rarely the first to develop. Therefore, the autoantibodies are a marker of risk for disease, but the disease may develop over many years.

Regulatory T-cells are thought to be important in the pathogenesis of disease, and regulatory T-cell gene signatures are associated with type 1 diabetes [21]. Additional analyses of T-cell function and development of T-cell assays will be important for monitoring for risk of autoimmunity and progression of disease.

34.1.4 Hormone Dysfunction

Once the autoimmune process is initiated, progressive failure of the affected gland occurs. In type 1 diabetes, markers of insulin release, insulin resistance, and glucose metabolism are associated with progression to dysglycemia once autoimmunity has occurred [22]. Hemoglobin A1c tends to rise within the normal range as diabetes develops in subjects with diabetes-related autoimmunity [23]. When followed with serial oral glucose tolerance tests, subjects are often noted to have impaired glucose tolerance, diabetes diagnosed on the basis of 2-h glucose alone, and then overt fasting hyperglycemia. However, some will have a normal hemoglobin A1c at the time of diabetes diagnosis based on oral glucose tolerance testing [24]. In subjects with 21-hydroxylase autoantibodies, progressive deterioration in adrenal secretion of cortisol and aldosterone is noted [25]. In thyroid disease, patients may initially present with compensated hypothyroidism and be relatively asymptomatic (elevated TSH but normal thyroid hormone levels) and progress to overt hypothyroidism.

Once sufficient tissue is destroyed, patients present with overt disease. At times, the presentation can be catastrophic and life-threatening such as with diabetic ketoacidosis (DKA) as the initial presentation for type 1 diabetes and adrenal crisis as the initial presentation of Addison's disease. C-peptide decline continues after diagnosis of diabetes in a biphasic fashion [26]. However, some patients with long-standing diabetes continue to secrete C-peptide, opening the door to treatment options even long after onset of overt disease.

34.2 Autoimmune Polyendocrine Syndrome Type 1 (APS-1)/Autoimmune Polyendocrinopathy Candidiasis and Ectodermal Dystrophy (APECED)

34.2.1 Etiology

APS-1 is an (mostly) autosomal recessive disorder historically defined by the presence of two of the following three conditions: hypoparathyroidism, adrenal insufficiency, and candidiasis [27]. The disorder is rare but has an increased frequency in certain populations such as Iranian Jews (1:9000), Sardinians (1:14,000), and the Finns (1:25,000) [28].

Mutations in the gene (located at 21q22.3) that encodes the AIRE protein are responsible for APS-1. It is inherited in a mostly autosomal recessive manner. However, a dominant negative mutation has been identified and associated with an atypical presentation of APS-1 [29]. The gene is a transcription factor which influences transcription by interacting with chromatin, not directly the DNA. It is expressed to a high degree in medullary thymic epithelial cells. These cells play an important role in T-cell maturation. It is hypothesized that the AIRE is important for the expression of self-antigens within the thymus and that this expression is important for the deletion of autoreactive T-cells (negative selection). Therefore, autoreactive T-cells are released into the periphery and can precipitate the autoimmune destruction of the organ to which the T-cells respond.

34.2.2 Clinical Presentation

Patients often present in infancy with chronic mucocutaneous candidiasis. Additional autoimmune diseases develop over time. Hypoparathyroidism often presents in early childhood at a median of 6 years of age. Adrenal insufficiency develops at a median of 10 years of age. The time from first disease component to the second component that would classify a patient as APS-1 can range from 2 to 20 years, which can profoundly delay the diagnosis of this complicated disorder. Autoimmunity affecting other organs can develop over time, and patients need to be monitored carefully for these disorders. Additional autoimmune endocrine disorders can occur including diabetes mellitus, hypothyroidism, and male and female hypogonadism [30–32]. Table 34.2 shows common autoimmune disorders associated with APS-1 and prevalence at various ages.

The autoimmunity associated with APS-1 is not limited to the endocrine disorders. Gastrointestinal symptoms are common and can include diarrhea and constipation. This has been hypothesized to be associated with autoimmune attack of the cells in the duodenum that produce cholecystokinin and serotonin and has been associated with autoantibodies against tryptophan hydroxylase. Patients develop autoimmune hepatitis, pernicious anemia, severe obstipation, and diarrhea. More rarely, patients develop autoimmune hypophysitis with resultant pituitary hormone deficiency, autoimmune disease affecting the lung, rheumatoid arthritis, and nephritis. Asplenia can also be present putting the patient at risk for the development of severe bacterial illness associated with pneumococcal infection. Therefore, subjects need to be carefully monitored for other organ system involvements [30–33].

The candidiasis associated with APS-1 is usually limited to the skin and mucosa. The candidiasis can be difficult to control, and treatment with antifungals may be required on a continuous basis. Patients may present with candidal esophagitis, which requires endoscopy to diagnose. Additionally, candida that is poorly responsive to treatment is a risk for carcinoma of the esophagus with a high morbidity and mortality. Therefore, aggressive control of candidal infections is recommended [33]. The candidiasis is associated with impaired T helper 17 cell response which is thought to increase the local production of antifungal chemokines and antimicrobial peptides [34]. This may be related to autoantibodies against key cytokines.

Patients with APS-1 may also manifest with ocular disease. Approximately 20% of patients develop keratoconjunctivitis. Keratoconjunctivitis often presents in childhood and puts the patient at risk for blindness. Ectodermal dystrophies include enamel hypoplasia, nail dystrophy, and calcium salt deposits in the tympanic membrane. The underlying cause of these abnormalities is not known.

Table 34.2 Autoimmune polyglandular syndrome type 1 (APS-1): disease associations

Component	Time of onset	Disease markers
Mucocutaneous candidiasis	Infancy	Symptoms and physical examination findings consistent with candidiasis
Hypoparathyroidism	Childhood	Low calcium with an inappropriately low or normal parathyroid hormone
Adrenal insufficiency	Childhood/adolescence	Elevated ACTH Decreased cortisol at baseline and in response to stimulation
Hypothyroidism	Adulthood	Elevated TSH, low thyroid hormone levels
Type 1 diabetes	Adulthood	Elevated glucose
Gonadal failure	Females: 20–30s Males: late manifestation	Elevated FSH/LH and low estradiol or testosterone
Autoimmune hepatitis	Prior to age 20 years	Elevated liver function tests Biopsy consistent with hepatitis
Intestinal malabsorption	Throughout lifespan	Constipation and/or diarrhea May complicated medical management of additional autoimmune disease
Celiac disease		Screened with tissue transglutaminase (TTG) IgA antibodies Confirmed on small intestinal biopsy
Pernicious anemia		Antibodies against parietal cells or intrinsic factor B12 deficiency
Asplenia	Throughout lifespan	Howell-Jolly bodies on peripheral blood smear
Ectodermal dystrophy	Childhood	Nail dystrophy Abnormalities of dental enamel Calcification of tympanic membranes
Keratoconjunctivitis	Childhood/adolescence	Diagnosed on eye examination

Data from Husebye et al. [30], p. 519

34.2.3 Diagnostic Evaluation

The diagnosis can be made on a clinical, immunologic, or genetic basis. Clinically, the disorder can be diagnosed when at least two of the three major disease components are present (candidiasis, adrenal insufficiency, and/or hypoparathyroidism). In subjects with a sibling with APS-1, the presence of one of the autoimmune or ectodermal components is diagnostic. However, when these criteria alone are used, a large proportion of subjects with genetically diagnosed APS-1 may be missed. Therefore, a high index of suspicion in addition to understanding the other components of the disorder can aid in the diagnosis of APS-1. Autoantibodies against interferon alpha and omega have been found in almost 100% of patients with APS-1 and are present prior to the development of autoimmune disease [35, 36]. These autoantibodies are rarely identified in healthy controls. Therefore, some have proposed the use of the autoantibodies to screen subjects with autoimmune disorders suspicious for APS-1. A positive result would be considered diagnostic of APS-1. These autoantibodies have the additional advantage of being present throughout the disease course. They have been identified in very young children prior to the development of the classic diagnostic criteria, and they have been identified in subjects with long-standing disease. Some authors propose screening for these autoantibodies and

following up positive results with genetic analysis of the AIRE gene [35]. Subjects with APS-1 require careful and close monitoring for the development of additional autoimmune diseases. Table 34.2 shows a proposed schema for follow-up and screening of patients with APS-1.

34.2.4 Outcomes and Possible Complications

Successful treatment of APS-1 requires close attention to detail and is largely dependent upon the underlying disorders that are present. Diseases such as autoimmune hepatitis and autoimmune pulmonary disease are associated with a particularly poor prognosis.

Given the chronic nature of their condition, the multiple organ systems that can be involved, and the need for frequent hospitalization and intensive treatment, subjects with APS-1 are at a high risk for associated psychiatric disease including depression and anxiety. Screening for such disorders is an important component of the care of patients with APS-1.

34.2.5 Treatment

The treatment of APS-1 is dictated by the clinical features for each patient. Generally, autoimmune endocrine disorders are treated by replacing the missing hormone. Chronic candidal infection may require treatment with systemic antifungals. Patients identified with asplenia require immunization and antibiotics to prevent overwhelming pneumococcal infection. Additional disease components are treated as they are identified. Diseases such as autoimmune hepatitis and autoimmune pulmonary disease may require treatment with systemic immunosuppressive medications.

34.3 Autoimmune Polyendocrine Syndrome Type 2 (APS2)

34.3.1 Etiology

The association of multiple autoimmune endocrine disorders was initially described by Schmidt as the coexistence of Addison's disease with type 1 diabetes and/or autoimmune hypothyroidism. Other autoimmune associations have been described including APS-3 (autoimmune hypothyroidism and another autoimmune disease not including type 1 diabetes or Addison's disease) and APS-4 (two or more organ-specific autoimmune diseases). These distinctions likely do not have clinical significance, and therefore, for the purposes of this discussion, we will use APS-2 to refer to any two organ-specific autoimmune diseases in one individual. Diseases both within and outside the endocrine system are associated with APS-2 including autoimmune thyroid disease (hypo- and hyperthyroidism), type 1 diabetes, Addison's disease, celiac disease, alopecia, vitiligo, autoimmune hypoparathyroidism, primary hypogonadism, myasthenia gravis, and pernicious anemia. Therefore, with the presence of one autoimmune endocrine disorder, practitioners need to be aware of the increased risk for additional diseases and screen with comprehensive history and physical and laboratory testing when indicated.

Patients with type 1 diabetes are at a high risk for the development of thyroid autoimmunity (20%) and disease (5–20%), depending upon duration of follow-up. Hypothyroidism is more common than hyperthyroidism. The presence of thyroid-related autoantibodies is associated with a progression to thyroid disease [20]. Autoimmunity associated with celiac disease is seen in approximately 10% of patients with type 1 diabetes. Approximately 30–50% of these patients have abnormalities on small intestinal biopsies that are consistent with celiac disease [37]. Specific HLA genotypes are associated with an increased risk for celiac disease in the population with T1D [38]. Genes outside the MHC such as *CTLA4* and *IL2RA* have been found in higher proportion of patients with CD and T1D than with either disease alone [39]. Adrenal autoimmunity is increased in patients with type 1 diabetes, such that approximately 1.5% of patients with type 1 diabetes are positive for 21-hydroxylase autoantibodies. Followed over time, approximately 30–40% of these patients go on to become adrenally insufficient [25, 40]. In this population, the risk for adrenal insufficiency is influenced by genes outside of the MHC, level of 21-hydroxylase autoantibody, gender, and presence of associated autoimmune conditions [25]. Patients with celiac disease are at an increased risk for the development of autoimmune thyroid disease, most commonly

hypothyroidism [41, 42]. Patients with autoimmune thyroid disease are also at risk for the development of celiac disease [43].

34.3.2 Clinical Presentation

Patients with APS-2 typically present with symptoms of an autoimmune endocrine disorder (type 1 diabetes, Addison's disease, or autoimmune thyroid disease) and are then found to have an additional autoimmune disease on the basis of more subtle symptoms of routine screening tests (e.g., testing TSH in a patient with type 1 diabetes). Clues to the development of additional autoimmune diseases can be identified on careful history, physical examination, and evaluation of the growth chart. Patients with type 1 diabetes developing adrenal insufficiency may present with decreasing insulin requirement, decreasing A1c, and increasing hypoglycemia. Patients developing hypothyroidism may have a decreased linear growth velocity. Celiac disease may manifest with weight loss and decreasing insulin requirements.

34.3.3 Diagnostic Evaluation

Given the increased rate of autoimmune diseases in patients with one autoimmune endocrine disease, careful screening is required for additional diseases. Current recommendations in patients with type 1 diabetes suggest annual screening for thyroid disease with at least measurement of a thyroid-stimulating hormone (TSH) level. Screening for celiac disease is recommended at onset of type 1 diabetes and with the presence of symptoms of celiac disease. There are no current recommendations for laboratory screening for Addison's disease in the populations with type 1 diabetes [44, 45]. Practice guidelines acknowledge the relationship between celiac disease and thyroid disease and suggest screening for celiac disease in patients with other autoimmune conditions that are associated with celiac disease such as hypothyroidism or a family history of celiac disease. Practitioners should also consider screening for thyroid disease in patients with celiac disease.

Screening for autoimmune diseases includes a careful history and physical examination to identify symptoms or signs of the underlying autoimmune condition. In pediatrics, we have the advantage of monitoring growth and development. Any abnormalities of growth or pubertal development in groups at high risk for the development of underlying autoimmune disease should serve as a red flag and warrant further evaluation including laboratory testing. Patients at high risk for the development of autoimmune disease include those with a previously diagnosed autoimmune disease such as type 1 diabetes, celiac disease, or thyroid disease and patients with chromosomal disorders associated with autoimmunity including Down and Turner's syndromes. The specific testing undertaken depends upon the underlying autoimmune disease and can include measurement of autoantibody levels, chemistry, and hormone levels. Depending upon these tests, additional testing including small intestinal biopsy (for celiac disease) and stimulation testing (for Addison's disease) may be necessary.

34.3.4 Outcomes and Possible Complications

Successful treatment of APS-2 requires close attention to detail and is largely dependent upon the underlying disorders that are present.

34.3.5 Treatment

Treatment focuses on treating the underlying autoimmune disease identified. Knowing the associations of these diseases allows for careful assessment for additional underlying autoimmune diseases, which has important clinical implications. For example, treatment of patients with undiagnosed adrenal insufficiency and hypothyroidism with levothyroxine may unmask the adrenal insufficiency and precipitate an adrenal crisis.

Treating the underlying autoimmune process to prevent the development of active disease is an area of active research in the setting of type 1 diabetes [46, 47]. Treatment has been targeted at each of the stages of autoimmune disease development, including genetic risk, presence of autoimmunity prior to development abnormalities of glucose metabolism, and presence of autoimmunity, impaired fasting glucose or impaired glucose tolerance, and early type 1 diabetes. The goals for the

treatment vary depending upon the stage of progression to diabetes. Treatment consortiums such as the TrialNet for type 1 diabetes conduct clinical trials in prevention of type 1 diabetes or preservation of C-peptide in patients newly diagnosed with type 1 diabetes [48].

The very earliest stages of disease are found in infants and young children. Therefore, a primary consideration is the safety of the treatment. Treatment trials include the use of hydrolyzed formulas at discontinuation of breast feeding [49], treatment with docosahexaenoic acid (and other components of fish oil), and treatment with oral insulin [50]. These trials are difficult to implement and monitor because the majority of people at high genetic risk for disease will never go on to develop disease. Therefore, many patients will be treated who will never develop disease. Additionally, disease develops over months to years. For this reason, many of these trials use markers of the autoimmune process as treatment end points.

People who have diabetes-related autoantibodies are already at an increased risk for the development of disease. Fewer subjects are needed to see treatment effect, and treatments can be slightly more toxic compared with interventions directed at antibody negative subjects. Large-scale trials have suggested that treatment with oral insulin in subjects who are first-degree relatives of patients with type 1 diabetes and have high levels of insulin autoantibodies may be effective in delaying the development of diabetes by approximately 4 years [51]. Follow-up confirmatory studies are underway. Additionally, treatment with glutamic acid decarboxylase 65 (GAD65) has been suggested to preserve C-peptide production in patients with newly diagnosed type 1 diabetes, without significant side effects [52]. Current trials are underway in patients with newly diagnosed type 1 diabetes and patients with positive GAD65 autoantibodies identified and followed through the TrialNet study.

Patients who are newly diagnosed with type 1 diabetes have been treated with immune-modulating drugs with the intent to preserve C-peptide function. Long-term studies of patients with type 1 diabetes have shown that persistent production of C-peptide is associated with decreased risk for long-term complications of type 1 diabetes. Patients stand to directly benefit from the sustained production of C-peptide. Taken together, treatments that have a higher toxicity are tolerated in patients newly diagnosed with type 1 diabetes compared with treatment directed at antibody-positive subjects without diabetes. At this stage, treatments are generally targeted toward the immune system with the goal preservation of C-peptide production. Anti-CD3 is a short-term T-cell-depleting therapy. Its use in humans was suggested by studies in animal models of type 1 diabetes. It has been used in clinical trials of patients with newly diagnosed type 1 diabetes and has demonstrated preservation of C-peptide production for up to 18 months. However, after the initial preservation of C-peptide production, the autoimmune process reemerges, and C-peptide production begins to decline again [53, 54]. Similarly, treatment with anti-CD 20 (a B-cell-specific antibody) has shown preservation of C-peptide production for approximately 1 year after treatment [55]. The treatments appear to temporarily halt the autoimmune process, but do not alter the underlying autoimmunity. It is possible that multiple or combination treatments will be required over a lifetime to permanently maintain C-peptide production.

34.4 Immunodysregulation Polyendocrinopathy Enteropathy X-Linked Syndrome (IPEX): A Brief Review

IPEX is a rare autoimmune endocrine disorder inherited in an X-linked fashion and associated with autoimmunity and immunodeficiency [56]. The underlying genetic defect is in the FOXp3 gene. FOXp3 is important for the development of regulatory T-cells. Without this gene, CD25+/CD4+ genes do not develop. These cells are regulators of CD4 effector T-cells in the periphery. Without these cells, fulminant autoimmunity can develop. Boys generally present as neonates with early onset type 1 diabetes and severe enteropathy resulting in diarrhea and profound failure to thrive. Patients are also at risk for severe dermatitis, hypo- or hyperthyroidism, anemia, thrombocytopenia, neutropenia, hepatitis, and kidney disease. As the genetic cause of the disease has been identified, it is now clear that the clinical phenotype is wider than previously appreciated and includes later onset of disease (into childhood) with a less fulmi-

nant presentation [57]. FOXp3 has been reported to be associated with recurrent intrauterine fetal demise of male infants [58]. As this is a rare condition, treatments are largely based on anecdotal evidence and have included immunosuppressive medications such as sirolimus and bone marrow transplantation. A report of two patients with low-intensity non-myeloablative conditioning hematopoietic cell transplantation showed stable engraftment of the transplanted cells [59]. Additional series shows an improvement in the disease even with chimeric T-cell populations, suggesting that less toxic preparatory regimens can be considered [60, 61].

Case Study

JF presented with type 1 diabetes at age 10 years. She was symptomatic at the onset of diabetes with polyuria, polydipsia, and a 5 kg weight loss. Initial laboratory testing was significant for an A1c of 10.5%, positive insulin, ZnT8 and GAD65 autoantibodies. Treatment with insulin in a basal bolus regimen was associated with improvement in her symptoms, weight gain, and decrease in her hemoglobin A1c to 8%. After 2 years of diagnosis, she was noted to have a decreased linear growth velocity and no pubertal development. Laboratory testing was obtained which was significant for a markedly elevated TSH of 200 uIU/mL, and she was diagnosed with hypothyroidism. Treatment was begun with levothyroxine at 75 mcg by mouth once daily. Approximately 1 week after treatment was initiated, JF developed pre-syncope and increased frequency of hypoglycemia. In retrospect, she had symptoms of salt craving and increased pigmentation. Laboratory testing was obtained and revealed an elevated ACTH and PRA with low random cortisol. Further testing confirmed an autoimmune process with positive 21-hydroxylase autoantibodies. Treatment with fludrocortisone and hydrocortisone was initiated.

34.5 Summary

Autoimmune endocrine disorders are common disorders in pediatric endocrinology and can coexist in recognized syndromes. Classification of subjects into specific syndromes allows for patient education related to disease and genetic risk, and providers can appropriately monitor their patients for disease. APS-1 is an autoimmune endocrine disorder that is inherited in an autosomal recessive manner. Patients are at risk for the development of multiple autoimmune diseases, and the disease is characterized by the presence of mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. The disease has a high morbidity and mortality, and multiple organ systems may be involved in the autoimmune process. APS-2 is inherited in a polygenic manner. It is more common in women than man and has a strong HLA association. Other more rare autoimmune endocrine syndromes include the IPEX syndrome. Prompt recognition of this syndrome may allow for lifesaving bone marrow transplantation.

Patients with a single autoimmune endocrine disorder are at an increased risk for the development of additional diseases and warrant close follow-up. Patients should be screened with a thorough history and physical examination for signs or symptoms of autoimmune diseases. Routine screening with laboratory tests may be indicated for certain disorders.

Review Questions

1. What is the genetic basis for APS-1?
   A. *AIRE*
   B. *CYP21A*
   C. *FOXP3*
   D. HLA class II
2. Which autoantibody is present in nearly 100% of patients with APS-1?
   A. 21-hydroxylase autoantibody
   B. Insulin autoantibody
   C. Interferon-alpha autoantibody
   D. Thyroid peroxidase autoantibody
3. What treatment has shown the most promise for prolonging the survival of patients with IPEX?
   A. Cytoxan
   B. Insulin
   C. Hematopoietic stem cell transplantation
   D. Pancreatic enzyme replacement

Answers

1. A
2. C
3. C

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