Autoimmune Endocrine Disorders 31

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Abstract

Autoimmune endocrine disorders are common conditions evaluated for and treated by pediatric endocrinologists. Recognition of the underlying autoimmunity associated with the disorders and disease associations is critical to providing appropriate care for these patients. Autoimmune endocrine disorders coexist in recognized syndromes known as the autoimmune polyendocrine syndromes (APS): APS-1 or autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED) and APS-2. More rare autoimmune endocrine disorders include the immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome. This rare disorder presents in infancy with type 1 diabetes and enteropathy. In this chapter, we will discuss the pathophysiology of the autoimmune process, the underlying genetics and disease associations of the autoimmune polyendocrine syndromes, and treatment and screening protocols and briefly touch on rare autoimmune endocrine disorders.

Keywords

Autoimmune polyendocrine syndrome type 1 • Autoimmune polyendocrine syndrome type 2 • Hypothyroidism • Hyperthyroidism • Type 1 diabetes • Celiac disease • Addison's disease

Introduction

Autoimmune endocrine disorders are common conditions evaluated for and treated by pediatric endocrinologists. Recognition of the underlying autoimmunity associated with the disorders and disease associations is critical to providing appropriate care for these patients. Autoimmune endocrine disorders coexist in recognized syndromes known as the autoimmune polyendocrine syndromes (APS): APS-1 or autoimmune polyendocrinopathy candidiasis and ectodermal dystrophy (APECED) and APS-2. More rare autoimmune endocrine disorders include the immunodysregulation polyendocrinopathy enteropathy X-linked

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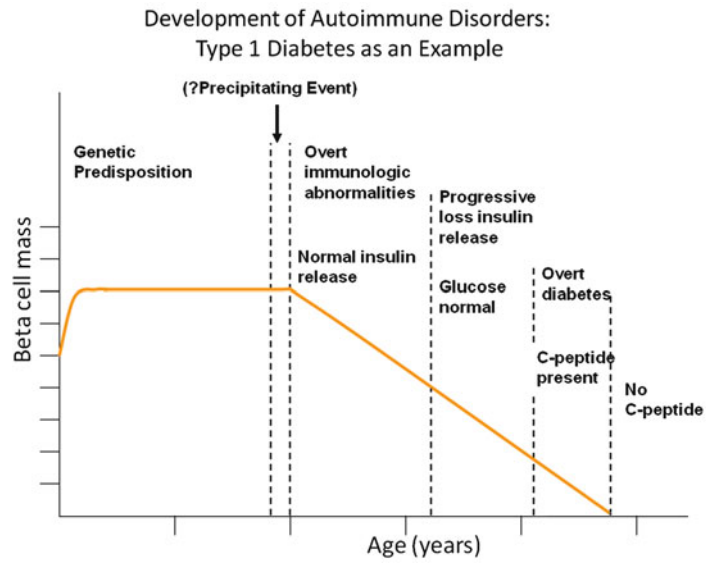

Fig. 31.1 Development of autoimmune disorders: type 1 diabetes as an example

(IPEX) syndrome. This rare disorder presents in infancy with type 1 diabetes and enteropathy. In this chapter, we will discuss the pathophysiology of the autoimmune process, the underlying genetics and disease associations of the autoimmune polyendocrine syndromes, and treatment and screening protocols and briefly touch on rare autoimmune endocrine disorders.

Natural History of Autoimmunity (Fig. 31.1)

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. This disease schema is a hypothesis of how autoimmune diseases develop and is obviously a simplification [1].

Much is known about the natural history of autoimmune disease through studies in infants and young children at risk for type 1 diabetes. Large-scale clinic trials such as the Diabetes Autoimmunity Study in the Young (DAISY) [2], the Finnish Diabetes Prediction and Prevention Project (DIPP) [3], and The Environmental Determinants of Diabetes in the Young (TEDDY) [4] studies enroll young children and infants who are at a heightened risk for the development of type 1 diabetes on the basis of family history of type 1 diabetes and/or presence of high-risk genetic markers for the disease prior to the development of autoimmunity associated with type 1 diabetes. The participants are then followed for diabetes-related autoimmunity and overt diabetes in an attempt to determine factors that are associated with disease development. These sorts of studies have increased our knowledge about the natural history of autoimmunity, and therefore, type 1 diabetes serves as a model for the development of other autoimmune diseases.

There are multiple genes that have been associated with the risk for autoimmune disease. The most consistent risk has been shown with the genes that make up the human leukocyte antigens (HLA) found on chromosome 6. Different HLA alleles have been associated with different autoimmune conditions. For example, the HLA DR3/DR4 has been associated with type 1 diabetes [5]. DR3 and DR4 are associated with autoimmune hypothyroidism [6] and DR3 with celiac disease [7], and DQ0602 is associated with protection from type 1 diabetes [8] and an increased risk for multiple sclerosis [9]. Other protective alleles for type 1 diabetes have also been identified including DP0402 in the setting of the high-risk DR3/

DR4 [10]. A particular allele of DR4, DRB1 0404, has been associated with Addison's disease [11]. 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). In addition to genetic risk, family history is known to play an important role in the development of autoimmune conditions. For example, in siblings of patients with type 1 diabetes, the presence of DR3/4 confers a greater risk for the development of type 1 diabetes compared with the risk in the general population with that HLA genotype. Moreover, 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% by 5 years of follow-up [12]. Thus, the risk for development of autoimmune disease can be additive.

Despite the strong genetic influence in development of autoimmune diseases, the genetic background does not tell the entire story related to the development of autoimmune 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. For example, it appears that timing of introduction to solid foods is an important risk for both type 1 diabetes, associated with early introduction of cereals, (<4 months) [13] and celiac disease associated with early introduction of gluten (<4 months) [14]. Vaccines have been shown to not be associated with the risk for type 1 diabetes [15]. Viruses and environmental toxins are also being investigated.

While the autoimmune destruction is thought to be mostly T cell mediated, the autoimmune process is marked by the presence of autoantibodies (antibodies against self-antigens) (Table 31.1). 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 [16], the persistence of the autoantibodies on multiple tests [17], and autoantibody level and affinity of autoantibodies for the antigens [18]. 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 antibodies [19]. Therefore, the autoantibodies are a marker of risk for disease, but the disease may develop over many years. T cell assays are currently under development. As our assays develop, we hope to be able to predict the development of autoimmune disease with greater accuracy.

Once the autoimmune process is initiated, progressive failure of the affected gland occurs. Markers of insulin release, insulin resistance, and glucose metabolism are associated with progression to type 1 diabetes once autoimmunity has occurred [20]. Hemoglobin A1c tends to rise within the normal range as diabetes develops in subjects with diabetes-related autoimmunity [21]. However, use of hemoglobin A1c to identify subjects at risk for type 1 diabetes as having normal glucose tolerance is not advised given that many people will have a normal hemoglobin A1c at the time of diabetes diagnosis based on oral glucose tolerance testing [22]. 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. In subjects with 21-hydroxylase autoantibodies, progressive deterioration in adrenal secretion of cortisol and aldosterone is noted [23]. In thyroid disease, patients may initially present with compensated hypothyroidism and be relatively asymptomatic

Table 31.1 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 Thyroglobluin autoantibodies	TSH Thyroid hormone levels
Hyperthyroidism	Thyroid stimulating immunoglobulin	TSH Thyroid hormone levels
Adrenal insufficiency	21-Hyroxylase 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

(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.

Autoimmune Polyendocrine Syndrome Type 1 (APS-1)/ Autoimmune Polyendocrinopathy Candidiasis and Ectodermal Dystrophy (APECED) (Table 31.2)

APS-1 is an autosomal recessive disorder historically defined by the presence of two of the following three conditions: hypoparathyroidism, adrenal insufficiency, and candidiasis. The disorder is rare but has an increased frequency in certain populations such as Iranian Jews (1:9,000), Sardinians (1:14,000), and the Finns (1:25,000) [24].

Over the last decade, the underlying genetic basis of APS-1 has been better defined. Mutations in the gene (located at 21q22.3) that encodes the AIRE protein are responsible for APS-1. The gene is a putative transcription factor and 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 an important transcription factor for the expression of self-antigens within the thymus and that this expression is important for the deletion of autoreactive T cells (negative selection) [24]. Therefore, in subjects who have inherited two defective copies of the AIRE gene, autoreactive T cells are released into the periphery and can precipitate the autoimmune destruction of the organ to which the T cells respond. The role of the AIRE gene in the mucocutaneous candidiasis and ectodermal dystrophy that is observed in patients with APS-1 continues to be defined.

Clinically, patients often present in infancy with chronic mucocutaneous candidiasis. Additional autoimmune diseases develop over time. Typically, the first autoimmune endocrine disorder that is identified is hypoparathyroidism which often presents in early childhood at a median of 6 years of age. The next disorder that develops is adrenal insufficiency, at a median of 10 years of age. However, it is important to note that the time from first disease component to the

Table 31.2 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		Diagnosed with TTG 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

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second component that would classify a patient as APS-1 can range from 2 to 20 years, thereby profoundly delaying 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 [15, 25, 26]. Table 31.2 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 syndromes. 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 [27]. Patients commonly develop autoimmune hepatitis, pernicious anemia, severe obstipation, and diarrhea. More rarely, patients can develop autoimmune hypophysitis with resultant pituitary hormone deficiency, autoimmune disease affecting the lung, rheumatoid arthritis, and nephritis. Asplenia can also be present and puts 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 involvement [15, 25, 26, 28].

The candidiasis associated with APS-1 generally is limited to the skin and mucosa. It is rarely systemic. The candidiasis can be difficult to control, and treatment with antifungals on a continuous

basis may be required. Patients may present with candidal esophygitis which may require endoscopy to diagnosis. Additionally, candida that is poorly responsive to treatment is a risk for carcinoma of the esophagus which has very high morbidity and mortality. Aggressive control of candidal infections is recommended [28].

Ocular disease can also develop in patients with APS-1. Approximately 20% of patients develop keratoconjunctivitis. Keratoconjunctivitis often presents in childhood and puts the patient at risk for blindness [29]. Ectodermal dystrophies are also present in patients with APS-1 and include enamel hypoplasia, nail dystrophy, and calcium salt deposits in the tympanic membrane. The underlying cause of these abnormalities is not known. The diagnosis can be made on a clinical, immunologic, and 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). Note that in subjects with a sibling with APS-1, 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. Recently, autoantibodies against interferon alpha and omega have been found in almost 100% of patients with APS-1 [27]. 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 [27]. Subjects with APS-1 require careful and close monitoring for the development of additional autoimmune diseases. Table 31.2 shows a proposed schema for follow-up and screening of patients with APS-1.

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 will 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.

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.

Autoimmune Polyendocrine Syndrome Type 2 (APS2)

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 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) have been described. 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 have been associated 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 [30]. Hypothyroidism is most commonly seen. Occasionally patients present with hyperthyroidism. The presence of thyroid-related autoantibodies is associated with a higher progression to thyroid disease [19]. 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 [31]. 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 [23, 32]. In this population, the risk for adrenal insufficiency is influenced by genes outside of the MHC (e.g., MIC-A), level of 21-hydroxylase autoantibody, gender, and presence of associated autoimmune conditions [23]. Patients with celiac disease are at an increased risk for the development of autoimmune thyroid disease, most commonly hypothyroidism [33, 34]. Conversely, patients with hypothyroidism are also at risk for the development of celiac disease [35].

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 thyroid-stimulating hormone (TSH). 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 screening for Addison's disease in the populations with type 1 diabetes [36]. 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. The specific screening 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.

Treatment focuses on treating the underlying autoimmune disease identified. Care should be taken related to the assessment for additional underlying autoimmune disease. For example, treatment of patients with undiagnosed adrenal insufficiency and hypothyroidism with thyroid medication 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. To date, no therapy is FDA approved outside of the research setting. 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 and abnormalities of glucose metabolism, not diagnostic of type 1 diabetes 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 have been established to identify subjects at risk for type 1 diabetes or

with newly diagnosed type 1 diabetes for randomized clinical trials in prevention of type 1 diabetes or preservation of c-peptide in patients newly diagnosed with type 1 diabetes [37].

The very earliest stages are usually found in infants and young children. Therefore, a primary goal is the safety of the treatment. Treatment trials include the use of hydrolyzed formulas at discontinuation of breast feeding [38] treatment with DHA (and other components of fish oil) and treatment with oral insulin [39]. 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 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.

Patients who have diabetes-related autoantibodies are already at an increased risk for the development of autoimmunity. Fewer subjects are needed to see an effect, and treatments can be slightly more toxic. 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 [40]. 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 [41]. 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. At this stage, treatments are generally targeted toward the immune system with the goal preservation of c-peptide production. Anti-CD3 is a T cell-depleting therapy, in which the T cell depletion is short term. 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. Treatment includes intravenous administration of the medication and has side effects related to the depletion of T cells. C-peptide production has been preserved 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 [42, 43]. Similarly, treatment with anti-CD 20 (a B cell-specific antibody) has shown preservation of c-peptide production for approximately 1 year after treatment [44]. The treatments appear to temporarily decrease the autoimmune process, but are not altering the underlying autoimmunity. It is possible that multiple or combination treatments will be required over a lifetime to permanently maintain c-peptide production.

Immunodysregulation Polyendocrinopathy Enteropathy X-Linked Syndrome (IPEX)

IPEX is a rare autoimmune endocrine disorder inherited in an X-linked fashion. The underlying genetic defect is in the FOXp3 gene [45]. 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 type 1 diabetes and severe enteropathy resulting in diarrhea and profound failure to thrive. Recent reports have shown that multiple autoantibodies can be present in these patients, suggesting a role for the CD25+/CD4+ T cells in regulation of B cells [46]. The association of these autoantibodies with development of autoimmune

diseases remains to be determined. As this is a rare condition, treatments are largely based on anecdotal evidence and have included immunosuppressive medications including sirolimus and bone marrow transplantation. A recent report of two patients with low-intensity non-myeloablative conditioning hematopoietic cell transplantation showed stable engraftment of the transplanted cells [47]. The authors proposed this method for preparation given that more intense regimens may be associated with significant toxicity in the already fragile infants.

Conclusion

Autoimmune endocrine disorders are common disorders in pediatric endocrinology. The autoimmune endocrine disorders 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 with a single-gene mutation responsible for disease. 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 associated with it, 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 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 thorough history and physical examination for signs or symptoms of autoimmune diseases. Routine screening with laboratory tests may be indicated for certain disorders.

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