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REVIEW

Type 1 diabetes and polyglandular autoimmune syndrome: A review

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Abstract

Type 1 diabetes (T1D) is an autoimmune disorder caused by inflammatory destruction of the pancreatic tissue. The etiopathogenesis and characteristics of the pathologic process of pancreatic destruction are well described. In addition, the putative susceptibility genes for T1D as a monoglandular disease and the relation to polyglandular autoimmune syndrome (PAS) have also been well explored. The incidence of T1D has steadily increased in most parts of the world, especially in industrialized nations. T1D is frequently associated with autoimmune endocrine and non-endocrine diseases and patients with T1D are at a higher risk for developing several glandular autoimmune diseases. Familial clustering is observed, which suggests that there is a genetic predisposition. Various hypotheses pertaining to viral- and bacterial-induced pancreatic autoimmunity have been proposed, however a definitive delineation of the autoimmune pathomechanism is still lacking. In patients with PAS, pancreatic and endocrine autoantigens either colocalize on one antigen-presenting cell or are expressed on two/various target cells sharing a common amino acid, which facilitates binding to and activation of T cells. The most prevalent PAS phenotype is the adult type 3 variant or PAS type Ⅲ, which encompasses T1D and autoimmune thyroid disease. This review discusses the findings of recent studies showing noticeable differences in the genetic background and clinical phenotype of T1D either as an isolated autoimmune endocrinopathy or within the scope of polyglandular autoimmune syndrome.

Key words: Autoimmune thyroid disease; Polyglandular autoimmune syndrome; Addison's disease; Susceptibility genes; Type 1 diabetes

Core tip: Type 1 diabetes (T1D) occurs in conjunction with several autoimmune endocrine and non-endocrine diseases. Recent studies have revealed noticeable differences in the genetic background and clinical phenotype of T1D either as an isolated autoimmune endocrinopathy or within the scope of polyglandular autoimmune syndrome. These findings are relevant for diagnostic and therapeutic procedures in daily practice as well as for the general understanding of endocrine autoimmunity.

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INTRODUCTION

Type 1 diabetes (T1D) is an endocrine disorder characterized by autoimmune destruction of insulin-producing pancreatic β-cells, which subsequently reduces insulin production and induces metabolic dysregulation[1-4]. Although T1D onset was once thought to be restricted to children and adolescents, it can occur at any age, with the highest rate of incidence below the age of 30 years[5-7]. Approximately 50 T1D susceptibility genes have been identified to date. These genes also carry a potential risk for various autoimmune diseases occurring simultaneously or within a narrow time interval and might explain to some extent why additional endocrine autoimmune diseases are comorbid in one third of all T1D patients[8-12]. These associated autoimmune disorders are either glandular diseases [*e.g.*, Addison's disease or autoimmune thyroid disease (AITD)] that lead to polyglandular autoimmune syndrome (PAS) or non-glandular autoimmune diseases (*e.g.,* rheumatoid arthritis or celiac disease)[13-15]. The variation in these comorbidities may hold the key to understanding the pathogenesis of autoimmune diseases, but also simultaneously complicates the diagnosis and treatment of T1D and is therefore of interest to both scientists and clinicians.

ISOLATED T1D

Approximately 5%-10% of all newly diagnosed patients with diabetes mellitus (nearly 400 million subjects worldwide) have T1D (20-40 million, accordingly)[5,16]. This number may be even higher as 5%-15% of all adults with type 2 diabetes are positive for pancreatic islet autoantibodies[17,18]. The age-adjusted incidence ranges from 0.1:100000/year (*e.g.,* China) to 40.9:100000/year (Finland), while the highest incidence rates are found in North American and European populations. Large studies confirmed a continuing rise of T1D incidence in Europe from 1989 through 2008 by approximately 3%-4% per year, which is higher than the average annual increase of 2.8%[19]. There is a subtle gender bias, where males have the highest incidence between 10-14 years of age and females have the highest incidence between the ages of 5 and 9 years[5,20,21]. The initial onset of T1D occurs primarily between the ages of 8 and 14 years, in close proximity to the start of puberty[22].

Clinical spectrum and diagnosis

Clinical symptoms, caused by the high glucose levels from T1D, develop quickly and range from chronic fatigue, weight loss, polydipsia and polyuria to symptoms of diabetic ketoacidosis (*e.g.,* nausea, acute abdomen or even coma). The diagnosis and differential diagnosis rely mainly on typical history and signs as well as measuring organ-specific autoantibodies directed against pancreatic islet cells, insulin, glutamate decarboxylase (GAD) and tyrosine phosphatase, which are positive in 95% of the cases at T1D onset. These pancreas autoantibodies may appear months or years before the clinical manifestation with various sensitivity, specificity and predictive relevance[23,24]. Positive titers of islet cell autoantibodies (ICAs), glutamic acid decarboxylase autoantibodies (GADAs), insulinoma-associated protein 2 autoantibodies (IA2As), insulin autoantibodies (IAAs) and the recently discovered zinc transporter 8 autoantibodies (ZnT8As) are important serologic diagnostic parameters. An early presence of autoantibodies is associated with a greater risk for T1D. The first antibodies to appear in young children are IAAs with a peak under the age of five years; a valid titer can only be measured before initiation of insulin therapy[25]. While titers of ICAs, ZnT8As and IAAs have been reported to decline after the onset of T1D, GADAs persist for years in the sera of diabetic patients independent of inflammatory β-cell destruction[26]. Therefore, measurement of GADAs is preferred in adults with late onset diabetes mellitus. ZnT8As can be found in about a fourth of T1D patients seronegative for ICAs, GADAs, IA2As and IAAs, and in approximately one third of patients with autoimmune disorders associated with T1D (Table 1)[27,28]. Considering the prevalence of organ-specific autoantibodies and their role in diagnosis of T1D, an autoimmune component in the disease manifestation seems undeniable.

Pathogenesis

Inflammatory infiltrates predominantly consisting of $CD4^+$ and $CD8^+$ lymphocytes and macrophages in the pancreatic tissue of patients with recent onset of T1D make an autoimmune etiology most likely[3,29-31]. In addition to direct killing of β-cells by natural killer cells, with a subsequent expression and presentation of autoantigens and a loss of peripheral immunologic tolerance, recently detected β-cell regeneration in children with T1D and β-cell persistence in older patients highlight a more complex pathogenesis that includes the involvement of cytokines, regulatory T cells and hormones[31-34]. Several studies have confirmed a higher cumulative risk for T1D in family members (Table 2). According to twin studies, the genetic predisposition and environmental effects might contribute 80% and 20%, respectively, to the clinical phenotype of T1D[35,36]. Further studies focusing on serologic and genetic characteristics of these patients revealed a multitude of susceptibility genes, antigens, serologic markers and environmental risk factors.

Genetics

Familial clustering (λs) imparts a relative risk (RR) for siblings of T1D-affected patients compared to the general

Table 1 Characteristics of the relevant autoantibodies in type 1 diabetes[125-134]

	Antigen	Sensitivity	Specificity	Percent at onset	Annotation
ICA	Islet cells	70%	99%	70%-90%	Single positivity similar predictive;
GADA	Glutamic acid decarboxylase (65 kDa)	65%-75%	99%	70%-80%	in combination ⩾ 3 increasing risk to
IA2A	Tyrosine phosphatase-related islet antigen 2	50%-90%	99%	50%-70%	approximately 90%; age independent
IAA	Proinsulin/insulin	74%	99%	30%-50%	Inverse correlation with age; measurement prior to insulin therapy required
ZnT8	C terminal domain of the zinc transporter 8	65%-75%	99%	60%-80%	Declines rapidly after onset of T1D

IAA: Insulin autoantibody; IA2A: Tyrosine phosphatase-related islet antigen 2 autoantibodies; ICA: Islet cell autoantibodies; GADA: Glutamic acid decarboxylase autoantibodies; T1D: Type 1 diabetes; ZnT8: Zinc transporter 8.

Table 2 Involvement of family members of patients with type 1 diabetes[5,27,135]

Affected family member	Presence of T1D
First degree relative (general)	5%-6%
Mother	2%
Father	7%
Monozygotic twin	30%-50%
Dizygotic twin	6%-10%

T1D: Type 1 diabetes.

population, amounting to RR = 15[37]. Several affected sibling pair linkage studies showed the importance of genetic predisposition and the association of T1D with polymorphisms in the specific human leukocyte antigen (HLA) loci on chromosome 6p21.3[38,39]. HLA class Ⅱ loci are assumed to be responsible for 40%-50% genetic risk[40,41]. HLA-DR3 or -DR4, which can be detected in approximately 95% of Caucasian Anglo-Saxon patients with T1D, partly reflect the distribution of the incidence among different countries and ethnicities in their genotype frequencies. Several studies graded the susceptibility of HLA class Ⅱ genotypes[42-45] as follows: the highest risk was found in DR3/4 heterozygotes, followed by DR4 homozygotes, DR3 homozygotes and DR4 heterozygotes combined with another DR allele[27]. Furthermore, many non-HLA polymorphisms that appear to make a smaller contribution to the manifestation of T1D have been identified[46]. Nevertheless, a concordance rate lower than 50% in monozygotic twins, a manifestation of T1D in 10% of the carriers of high-risk genes and a 15-fold difference in the disease incidence among European Caucasians indicates that genetics alone cannot explain disease onset[8,47,48]. In contrast, an increase in patients with low-risk or protective HLA genotypes emphasizes the importance of environmental factors such as viral infections, nutrition and chemicals or epigenetics, respectively[49-52].

ASSOCIATION OF T1D WITH OTHER ENDOCRINOPATHIES

Additional or associated autoimmune glandular and non-glandular diseases in patients with T1D have been described and frequently involve organ-specific as well as systemic autoimmunity. The following autoimmune diseases are listed in the order of their frequency: autoimmune thyroid diseases (AITD, 15%-30%), autoimmune type A gastritis (15%), pernicious anemia (10%), celiac disease (4%-9%), vitiligo (1%-7%), rheumatoid arthritis (1.2%), systemic lupus erythematosus (1.15%), autoimmune adrenal failure or Addison's disease (0.5%) and multiple sclerosis (0.2%) (Table 3)[53-60]. In addition to a common environment, many overlapping risk factors for T1D and other autoimmune diseases have been identified. While a role for HLA class Ⅰ -recognizing CD8 T cells has been known to affect T1D and celiac disease, recent studies also showed a joint susceptibility for these diseases in HLA class Ⅱ[61]. HLA-DQ2 can be found in 90% of patients with celiac disease and in 55% of patients with T1D, while HLA-DQ8 is present in approximately 10% and 70%, respectively[62]. In patients with HLA-DQ2-DQ8 heterozygosity, a transdimer (DQ2α/8β) binds a gliadin peptide and T1D-specific antigens, which implicates both gluten and the gut microbiome as additional factors or triggers for autoimmune diseases, respectively[63-66]. Because the co-occurrence of non-glandular immunopathies such as autoimmune gastritis and pernicious anemia may lead to an atypical clinical presentation and additional discomfort, early and regular screening for serologic parameters (*e.g.*, parietal cell antibodies) and red blood cell count is recommended[67].

The manifestation of additional glandular autoimmune diseases in association with T1D has recently become of particular interest for research on the common pathogenesis of general autoimmunity. PAS characterized by a combination of at least two autoimmune endocrinopathies can be classified into a juvenile form (PAS type Ⅰ) and an adult form, which is then subdivided according to the specific constellation of autoimmune glandular diseases (PAS types Ⅱ-Ⅳ)[68-70].

T1D WITHIN THE SCOPE OF JUVENILE PAS TYPE I

PAS type Ⅰ, also known as Whitaker's syndrome, autoimmune polyendocrinopathy-candidiasis-ectodermal-

Table 3 Prevalence of associated autoimmunity in patients with type 1 diabetes[15,55,56,60,97,100,136-143]

Associated disease	Patients with type 1 diabetes		General population	
	Prevalence of organ-specific Abs	Overt disease	Prevalence of organ-specific Abs	Overt disease
Type 1 diabetes	ICA in 85%-90%	100%	ICA in 1%-3 %	0.1%-1.0%
Hashimoto's thyroiditis	TPO Abs in 15%-30%	10%-20%	TPO Abs in 2%-10%	0.5%-9.0%
Graves' disease	TSH-R Abs in 1%-18%	3%-6%	TSH-R Abs in 1%-2%	0.1%-2.0%
Addison's disease	21-OH Abs in 0.7%-2.0%	0.5%-0.8%	21-OH Abs in 0.6%	0.005%-0.140%
Autoimmune hypophysitis and/or hypopituitarism	Pituitary Abs in 3.6%	0.4%-0.9%	Pituitary Abs in 0.5%	0.24%-0.80%
Autoimmune type A gastritis and pernicious anemia	Gastric parietal cell Abs in 13%-25%	5%-10% (2%-6%)	Gastric parietal cell Abs in 2.5%-12.0%	2% (0.15%-1.00%)
Celiac disease	Transglutaminase Abs in 8%-12%	1%-9%	Transglutaminase Abs in 0.5%-1.0%	0.50%

Abs: Antibodies; ICA: Islet cell antibodies; TPO: Thyroperoxidase; TSH-R: Thyrotropin receptor antibodies; 21-OH: 21 Hydroxylase.

dystrophy or multiple endocrine deficiency autoimmune candidiasis syndrome, is a hereditary disorder with disease manifestation that occurs in a characteristic order at an early age. Mucocutaneous candidiasis is typically the first of the three major components to occur, typically prior to five years of age. Before the age of ten years, hypoparathyroidism becomes apparent and precedes Addison's disease, which is usually the last disorder to appear (in many cases before the age of 15 years). By definition, at least two of these major components must be present for PAS type Ⅰ. Additional disorders were described that occurred prior to the fifth decade[71,72]. T1D was found in 12%-33% of all patients with PAS type Ⅰ[72,73]. Several studies have suggested that a young age of clinical onset correlates with the manifestation of multiple concomitant autoimmune diseases[74,75]. As a monogenetic disease with autosomal recessive inheritance caused by mutations in the autoimmune regulatory gene on chromosome 21, the prevalence of PAS Ⅰ varies highly between ethnicities ranging from 1:6500 in Iranian Jews to 1:10000000 in the Japanese population, with a female/male ratio of 0.8-2.4[76-78].

Screening for the co-occurrence of T1D in patients with PAS Ⅰ is less effective. This is because the positive predictive value of ICAs and GAD65 autoantibodies is only 27%, whereas 18%-28% of PAS type Ⅰ patients without T1D have islet cell autoantibodies present[73,79]. This peculiarity led to the hypothesis that the detected autoantibody epitopes differ from those in patients with isolated T1D and that a limited, subclinical autoimmune reaction within the pancreas may exist without causing an overt clinical manifestation[73,80]. A novel β-cell antigen, initially identified as a 51 kDa protein, was found to be aromatic-L-amino-acid decarboxylase[81-83]. Though no correlation of T1D manifestation in PAS and anti-aromatic-L-amino-acid decarboxylase autoantibodies has been found yet, its high prevalence in PAS type Ⅰ-associated diseases (*e.g.,* vitiligo and autoimmune hepatitis) warrants further research on its role in disease pathogenesis of autoimmune disorders[82]. Similar to isolated T1D, the combination of autoantibodies in polyendocrinopathies has been suggested to provide a higher predictive value than any isolated autoantibody.

T1D WITHIN THE SCOPE OF THE ADULT PAS (TYPES Ⅱ-Ⅳ)

T1D is the most frequent disorder of the PAS and is often the first disease to appear. The exact immunopathogenesis has not been fully elucidated, but several studies provide evidence for common immunologic mechanisms induced by environmental factors in a background with genetic polymorphisms[84-86]. The frequent finding of combined manifestations of autoimmune glandular diseases led to a sub-classification for adult PAS as follows[68,87]: (1) PAS type Ⅱ: Addison's disease in combination with at least one additional autoimmune endocrinopathy (*e.g.,* T1D); (2) PAS type Ⅲ: autoimmune thyroid disease in combination with T1D but excluding Addison's disease; (3) PAS type Ⅳ: combination of at least two autoimmune endocrinopathies but excluding PAS types Ⅰ-Ⅲ.

Clinical spectrum and diagnosis of T1D within PAS types Ⅱ-Ⅳ

In approximately 40%-50% of patients with Addison's disease, additional autoimmune glandular diseases occur and become overt as PAS type Ⅱ. Of these, T1D is apparent in 12%-24%[88-90]. Autoantibodies directed against the adrenal cortex are found in 0.7%-3.0% of T1D patients. Although T1D often develops before Addison's disease, GAD65 antibodies are detected in 5%-7% of patients with Addison's disease but without T1D, thus a thorough follow-up should be performed in islet cell antibody-positive patients. The concomitant presence of Addison's disease and T1D leads to frequent hypoglycemia due to decreased gluconeogenesis and increased insulin sensitivity. Thus, autoimmune-induced adrenal failure should be considered in patients with T1D suffering from unexplained recurrent hypoglycemia and fatigue, whereas insulin therapy combined with cortisol substitution warrants close monitoring during treatment of T1D patients with adrenal failure.

PAS type Ⅲ is the most frequent subtype of poly-glandular autoimmune diseases, containing 41% of the possible endocrine component combinations[68]. The co-occurrence of autoimmune-induced hypothyroidism (generally caused by chronic lymphocytic Hashimoto's

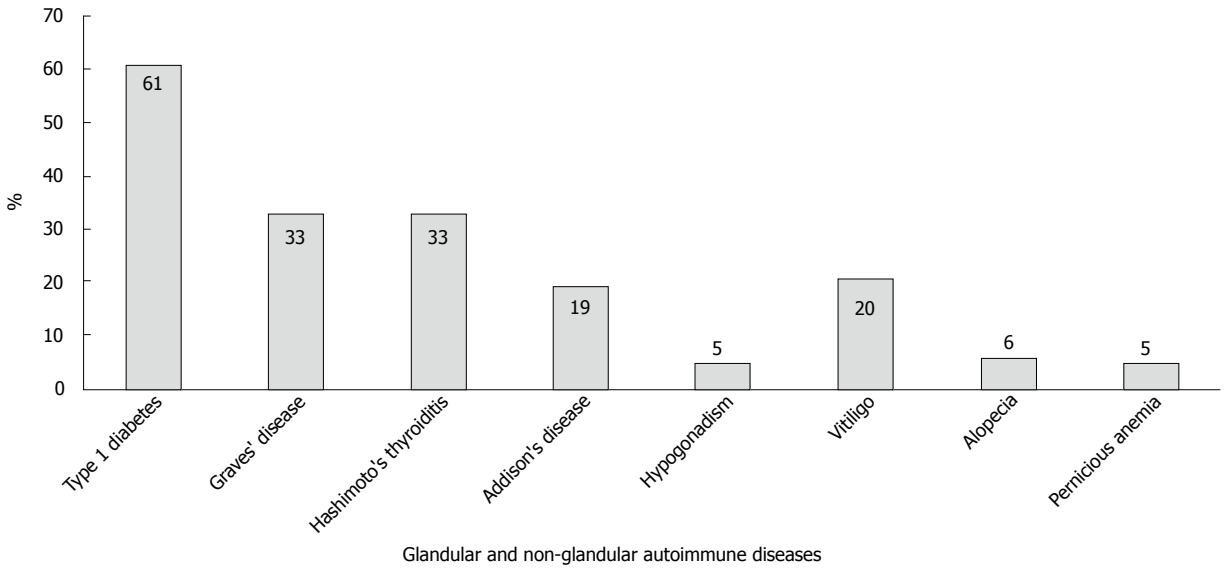

Figure 1 Endocrine and non-endocrine autoimmune diseases in patients with polyglandular autoimmune syndrome. The prevalence of glandular (dark grey) and non-glandular (light grey) autoimmune diseases in the 151 patients with adult polyglandular autoimmune syndrome (PAS) followed at the Johannes Gutenberg University Medical Center.

thyroiditis) and T1D is often accompanied by hypoglycemia due to increased insulin sensitivity. Hypothyroidism leads to a reduction in glucose resorption in the duodenum and glucose release from the liver. Because patients exhibit a decreased appetite and intake of calories, the risk for hypoglycemia is significantly enhanced[91-93]. During the hypothyroid phase, the insulin dosage should be carefully evaluated and a reduction by approximately 20%-25% for 3-4 wk is recommended. After substitution with levothyroxine, the baseline insulin dosage may be administered again, after the patient becomes biochemically euthyroid. In hypothyroid children, chronic hypoglycemia and decreased food intake frequently lead to growth disorders. Either anti-thyroid peroxidase and/or antithyroglobulin autoantibodies are present in 19%-24% of T1D patients, whereas hypothyroidism (subclinical with normal free thyroid hormone levels but pathologically increased baseline serum thyroid-stimulating hormone) is observed in 10%-20% of patients[12,94-96]. In comparison, subclinical and overt hyperthyroidism occur less frequently (3% and 6%, respectively)[97]. Overt hyperthyroidism is accompanied in 50% of the cases by glucose intolerance and in 3% of the cases by overt diabetes. The impaired glucose tolerance is due to decreased insulin sensitivity and decreased hepatic storage of glycogen, whereas both secretion of glucagon and intestinal glucose absorption are enhanced. Thus, hyperthyroidism increases glucose resorption and hepatic glucose release leading to hyperglycemia. In T1D patients, this leads to insulin resistance and an increased release of fatty acids causing ketoacidosis[53,91,98]. T1D usually manifests at a very young age. Moreover, in 60% of PAS type Ⅲ patients, Graves' hyperthyroidism may occur prior to T1D, as has been reported in Japanese populations, usually within a time period of less than ten years[99]. Onset of T1D in patients with Graves' disease and Hashimoto's thyroiditis occurred at a mean age of 34 years in 0.78% and 1.17% of cases, respectively[100]. ZnT8As, and especially GADAs, are observed more frequently in PAS type Ⅲ than in isolated T1D, while IA2As may indicate a slow onset of T1D[99]. In addition, in patients with T1D and PAS type Ⅲ, gastric parietal cell and adrenocortical autoantibodies have been observed in 16.8% and 5.1% of cases, respectively[96].

PAS type Ⅳ is a very heterogeneous and less well-defined group of polyglandular autoimmune diseases. It is frequently incorrectly published that this syndrome is defined as the combination of a monoglandular autoimmune disease (*e.g.,* T1D) with a non-glandular autoimmune disease (*e.g.,* autoimmune gastritis or celiac disease). In PAS type Ⅳ, pituitary antibodies have been detected in 3.6% of T1D patients, and clinically overt pituitary failure was noted in 0.9%[101]. Aside from PAS type Ⅰ, the combinations of T1D with autoimmune hypopituitarism or hypergonadotrophic hypogonadism as rare forms of PAS type Ⅳ have an estimated prevalence of < 1% and are rarely described in the literature[102,103].

Our own findings

In a screening of 471 consecutive T1D patients that were followed at the endocrine outpatient clinic at the Johannes Gutenberg University Medical Center, multiple glandular involvement and PAS type Ⅲ were found in 27% (n = 127) and 10%, respectively[104]. Subsequent prospective screening of 15000 consecutive patients with monoglandular autoimmune disease (*e.g.,* T1D) revealed a high prevalence (1%) of patients with the adult PAS types Ⅱ-Ⅳ, with a female bias of 75%. Figure 1 shows the various spectrums of autoimmune diseases registered in our PAS cohort. Significant male and female biases were noted for T1D and Hashimoto's thyroiditis, respectively. T1D manifested early (mean: 27.5 years), whereas other component diseases appeared later, ranging from an age

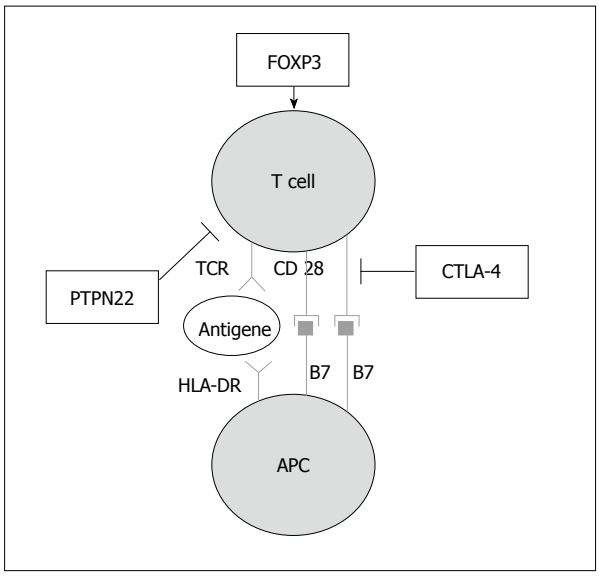

Figure 2 Immunologic synapse. This schematic depicts T cell activation and how it is influenced by expression of common susceptibility genes. Shared susceptibility genes for autoimmune thyroid disease and type 1 diabetes are involved in the immunological synapse. HLA-DR molecules present autoantigens to T cells, CTLA-4 expression suppresses T cell activation, PTPN22 expression negatively influences the T cell receptor (TCR) signaling pathway and FOXP3 expression regulates the differentiation of regulatory T cells (modified according to ref.[124]). APC: Antigen presenting cell; CTLA-4: Cytotoxic T lymphocyte antigen 4; HLA: Human leukocyte antigen; PTPN22: Protein tyrosine phosphatase non-receptor type 22; FOXP3: Forkhead box protein P3.

of 36.5-40.5 years. T1D was also the first component disease of adult PAS in half of the patients (48.3%), whereas Graves' disease (19.2%), Hashimoto's thyroiditis (17.2%), Addison's disease (14.6%) and vitiligo (12.6%) were less likely to be the first component disease. The predominant frequency of the coexistence of T1D and AITD was confirmed in our large collective. The time interval between manifestations of the first and second endocrinopathies varied considerably, with the longest time intervals between T1D and AITD, and a short time interval between Addison's disease and AITD[105].

GENETICS OF THE ADULT PAS TYPES Ⅱ-Ⅳ

Unlike the 1:1 gender ratio of isolated T1D and PAS type Ⅰ, there is a clear female bias of 3:1 in adult PAS, with a prevalence of 1:20000[13,104,106]. The incidence of adult PAS is approximately 1:100000/year and has a peak in the third or fourth decade of life. For a majority of the glandular autoimmune disorders, common susceptibility genes have been identified, including polymorphisms in protein tyrosine phosphatase non-receptor type 22, cytotoxic T lymphocyte antigen 4 (CTLA-4), MHC class I polypeptide-related sequence A, and HLA (Table 4, Figure 2). Thus, the association of endocrine autoimmune diseases is primarily due to a common genetic predisposition. The HLA class Ⅱ haplotypes

Table 4 Odds ratio of susceptibility genes for autoimmune endocrinopathies[117,144-160]

	T1D	HT	GD	AD
HLA-DR3	3.5	3.7	2-4	5
MICA	1.6	2.5	2	7
PTPN22	1.8	1.6	1.6	1.5
CTLA-4	1.5	5	1.5	1.8

AD: Addison's disease; CTLA-4: Cytotoxic T lymphocyte antigen 4; GD: Graves' disease; HLA: Human leukocyte antigen; HT: Hashimoto's thyroiditis; MICA: MHC class I polypeptide-related sequence A; PTPN22: Protein tyrosine phosphatase non-receptor type 22; T1D: Type 1 diabetes.

DRB1*03-DQA1*0501-DQB1*0201 and DRB1*04-DQA1-0301-DQB1*0302 have been reported to be associated with isolated T1D as well as with T1D within the scope of adult PAS[10,107]. This joint susceptibility for both T1D and AITD has been demonstrated in both Caucasians and in Asians[108-112]. CTLA-4 A/G49 single nucleotide polymorphisms (SNP) confer susceptibility to PAS type Ⅲ[113,114]. In particular, the CTLA-4 SNP rs3087243 (+ 6230 G > A) variant seems to predispose patients to a combined manifestation of T1D and Graves' disease[115]. The 1858 C→T substitution in the protein tyrosine phosphatase non-receptor type 22 gene is associated with AITD, isolated T1D and PAS type Ⅲ and the G1,123C SNP is associated with T1D and AITD in Asians[116-119]. Additionally, a SNP in the forkhead box P3 (*FOXP3*) gene on the arm of the X chromosome has been associated with increased susceptibility to PAS type Ⅲ in Caucasians[113]. A mutation in *FOXP3* has also been shown to be the susceptibility gene in the extremely rare immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome[120]. Typically, T1D is associated with severe enteropathy, hypothyroidism and autoimmune skin diseases such as psoriasis, neurodermitis and psoriasis vulgaris[121]. There is a large variability in the organs affected by the additional autoimmune diseases in the severe IPEX syndrome and many patients die in infancy. Because *FOXP3* plays an important role in the function of regulatory T cells, a recent study suggested a similar CD25-correlated pathogenesis in isolated T1D and T1D within the context of the IPEX syndrome (Table 5)[122,123].

CONCLUSION

In isolation as a monoglandular disease, or within the larger context of PAS, the manifestation of T1D justifies an extensive serologic and functional screening for additional autoimmune glandular and gastrointestinal diseases both in patients with T1D of recent onset as well as every two years during patient follow-up (Figure 3). In particular, in families with clustering of T1D patients or in families of patients with PAS, the risk for associated autoimmune diseases and endocrine or autoimmune involvement of the first-degree relatives is significantly

Table 5 Polyglandular autoimmune syndromes[13,68,78,161-166]

	PAS Type Ⅰ	PAS Type Ⅱ-Ⅳ	IPEX
Onset	Childhood	Adulthood	Infancy
Incidence	< 1:100000/yr	1–2:100000/yr	Extremely rare
Male/Female ratio	3:04	1:03	Male >> Female
Genetics	Monogenetic (AIRE)	Polygenetic	X-linked (FOXP3)
Autoantibodies	Anti-interferon-α/ω antibodies 100%, additional Abs	Organ-specific Abs depending on the autoimmune components	ANA (42%) SSA (25%) TG Abs (25%)
Prevalence of T1D	2%-33%	40%-60%	80%
Additional autoimmune endocrine components	Hypoparathyroidism (80%-85%) Addison's disease (60%-70%) Hypogonadism (12%) Autoimmune thyroid disease (10%)	Autoimmune thyroid disease (70%-75%) Addison's disease (40%-50%) Hypoparathyroidism (0%-5%) Hypogonadism (0%-3%) Hypopituitarism (0%-2%)	Autoimmune thyroid disease (25%)
Concomitant non-endocrine diseases	Mucocutaneous candidiasis (70%-80%); autoimmune hepatitis; autoimmune gastritis; alopecia areata; vitiligo; keratoconjunctivitis	Autoimmune gastritis; pernicious anemia; neurodermitis; alopecia areata; myasthenia gravis; systemic lupus erythematosus; rheumatoid arthritis; autoimmune hepatitis	Malabsorption; autoimmune skin diseases; multiple sclerosis

Abs: Antibodies; AIRE: Autoimmune regulatory gene; ANA: Anti-nuclear antibodies; FOXP3: Forkhead box protein P3; IPEX: Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; PAS: Polyglandular autoimmune syndrome; TG: Transglutaminase; T1D: Type 1 diabetes.

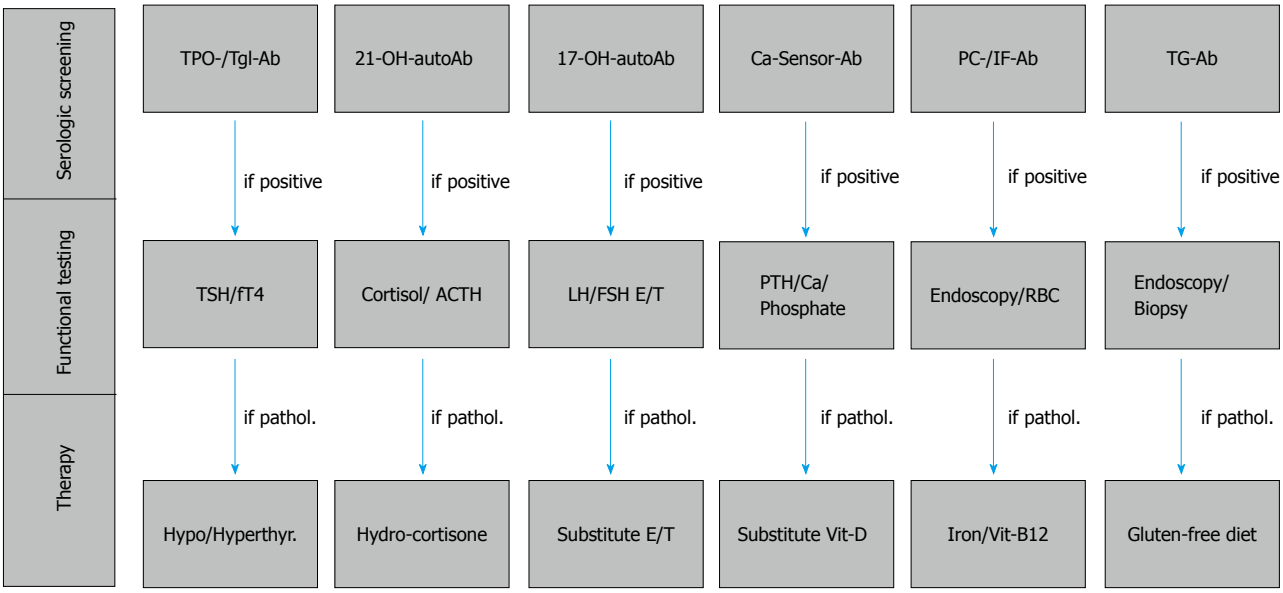

Figure 3 Serologic and functional screening in patients with type 1 diabetes. The serologic and functional screening for associated autoimmune diseases in patients with type 1 diabetes (T1D) performed at the onset of T1D and during follow-up appointments every two years. After diagnosis of thyroid dysfunction, adrenal failure, primary hypogonadism, hypoparathyroidism, type A autoimmune gastritis with or without pernicious anemia and celiac disease, substitution proceeds with levothyroxine, hydrocortisone, estradiol or testosterone, vitamin D, iron tablets and vitamin B12 intramuscularly, with a strict gluten-free diet. In contrast, hyperthyroidism due to the autoimmune Graves' disease will be managed first with the administration of anti-thyroid drugs (*e.g.*, methimazole). Ab: Antibody; ACTH: Adrenocorticotropic hormone; Ca: Calcium; Ca-Sensor: Calcium-sensing receptor; E: Estradiol; FSH: Follicle-stimulating hormone; fT4: Free thyroxine; Hypo: Hypothyroidism; Hyperthyr: Hyperthyroidism; IF: Intrinsic factor; LH: Luteinizing hormone; PC: Parietal cell; PTH: Parathyroid hormone; RBC: Red blood cell count; T: Total testosterone; TG: Transglutaminase/deaminated anti-gliadin; Tgl: Thyroglobulin; TPO: Thyroid peroxidase; TSH: Thyrotropin; Vit: Vitamin; 17-OH: 17-hydroxylase; 21-OH: 21-hydroxylase.

high. Within a few years, approximately one third of T1D patients will develop thyroid autoantibodies and thyroid dysfunction leading to PAS type Ⅲ. Furthermore, in subjects with either monoglandular T1D or the relatively rare autoimmune adrenal failure, organ-specific autoantibody screening and functional testing will help identify both patients at risk for developing PAS, as well as subclinical PAS that may already be present. Clinicians should pay particular attention to autoimmune endocrinopathies, (*e.g.,* Addison's disease or AITD), which are associated with T1D and strongly impact the patients' treatment with insulin. Thus, adrenal 21-hydroxylase autoantibodies should be assayed in all patients with T1D and GAD antibodies should be examined in all patients

with Addison's disease for early identification of subjects with a preclinical manifestation of a PAS. In conclusion, management of T1D within the context of PAS requires professional oversight and intervention provided in specialized centers for autoimmune endocrine and metabolic disorders.

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