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Autoimmune polyglandular diseases

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Autoimmune polyglandular diseases (APD) are defined as the presence of two autoimmune −induced endocrine failures. With respect to the significant morbidity and potential mortality of APD, the diagnostic objective is to detect APD at an early stage, with the advantage of less frequent complications, effective therapy and better prognosis. This requires that patients at risk be regularly screened for subclinical endocrinopathies prior to clinical manifestation. Regarding the time interval between manifestation of first and further endocrinopathies, regular and long-term follow-up is warranted. Quality of life and psychosocial status are poor in APD patients and involved relatives. Familial clustering is high in patients with APD. Considering the high incidence of one or more endocrinopathies in first-degree relatives of patients with APD, family members should be regularly screened since they may also develop autoimmune endocrinopathies. Multidisciplinary management of these multiplex families in specialized centers is warranted.

Introduction

The autoimmune polyglandular diseases (APD) are divided in a juvenile type 1 and an adult type 2 [1]. They form different clusters of autoimmune disorders [2]. APD is defined by the occurrence of two or more autoimmune endocrine disorders in the same individual including Graves' disease (GD),

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Hashimoto's thyroiditis (HT), type 1 diabetes (T1D), Addison's disease (AD), and premature hypogonadism [3]. Several non-endocrine disorders such as myasthenia gravis, celiac disease, pernicious anaemia, vitiligo, and alopecia may occur in these patients [4–6]. The coexistence of adrenal failure with either autoimmune thyroid disease (AITD) and/or T1D is defined as Schmidt's syndrome or Carpenter's syndrome. Type two APD is more varied in its manifestations than type 1, also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, APECED. The latter is characterized by three specific disorders, i.e. chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism, and AD [7,8]. Other endocrine and non-endocrine autoimmune disorders either may be present or will develop later (Table 1). APD1 manifests in infancy or early childhood. It is a monogenic disease with autosomal recessive inheritance caused by mutations in the *autoimmune regulatory gene* (*AIRE*) on chromosome 21 [2,7]. In contrast, APD2 shows a complex inheritance pattern [2].

APD is a rare disease. In this review, we will focus on the more common APD2 which prevalence is 1:20 000 [2]. It is more frequently encountered in women (male-to-female ratio 1:3 [9]). This syndrome has a peak incidence at ages 20–60, mostly in the third or fourth decade. It is common for multiple generations to be affected by one or more component diseases and family members of patients are often affected [10,11]. While there is some correlation between the ages of onset of one polyglandular syndrome illness with another, many years may separate the onset of different diseases [12,13]. There are many common themes linking each of these individual illnesses. All the disorders resulting in tissue destruction appear to have a prolonged phase of cellular loss preceding overt APD.

Pathophysiology

Cell-mediated immune processes are important in APD. Lymphocyte infiltrations of the various glands are associated with functional loss of epithelial cells with scarring. The cellular defect is associated with abnormal balances in cytokine production by T cells. The subgroups of T helper cells – Th1 and Th2, natural killer cells – produce a different profile of cytokines. Th1 cells secrete interferon-γ, interleukin 2, and tumour necrosis factor ά, whereas Th2 cells secrete interleukins 4, 5, and 10. A

Table 1
Autoimmune polyglandular disease.

Sub-type	Juvenile	Adult
Onset	Childhood	Adulthood
Gender ratio (male/female)	3:4	1:3
Prevalence	1:100,000	1:20,000
Serology	Interferon α/ω-Ab	Organ-specific Ab
Endocrine components	Hypoparathyroidism (80–85%)	Autoimmune thyroid disease (70–75%)
	Addison's disease (60–70%)	Type 1 diabetes (40–60%)
	Type 1 diabetes (2–33%)	Addison's disease (40–50%)
	Hypogonadism (12%)	Hypoparathyroidism (≤5%)
	Autoimmune thyroid disease (10%)	Hypogonadism (≤3%)
		Hypopituitarism (≤2%)
Non - endocrine components	Mucocutane candidiasis (70–80%)	Autoimmune gastritis
	Moniliasis	Vitiligo
	Ectodermal dystrophy	Alopecia
	Enamel hypoplasia	Urticaria
	Keratitis	Psoriasis
	Hyposplenism	Celiac disease
	Tubular-interstitial nephritis	Rheumatoid arthritis
	Autoimmune hepatitis	Autoimmune hepatitis
	Atrophic gastritis	Pernicious anemia
	Alopecia	Systemic lupus erythematosus
	Vitiligo	Myasthenia gravis
	Keratoconjunctivitis	Sicca-/Sjögren-syndrome
		Neurodermitis
		Pemphigus
		Atopic eczema

polarized Th2 response is associated with GD and Th1 with T1D. In contrast, APD1 results from biased Th2 immune responses to self-antigens and defective protective Th1 responses against invasion of yeast Candida albicans [14]. Table 2 shows the localisation of the various autoantigens and corresponding component diseases of APD. Viral and bacterial aetiology for autoimmunity has been proposed [15]. A dominance of T-helper cells and a deficiency of T suppressor cells have been demonstrated for endocrine autoimmunity [16]. Also, a hypothesis for the pathogenesis of APD has been presented [12]. Accordingly, a genetically predisposed person might develop an autoimmune process after initiation by an infectious agent. This might initiate *via* cross reactivity in the area of antigen presenting MHC molecules a T-helper-type-2-dependent immune process which is primarily of humoral origin and partly local. This immune process probably chromicise due to deficient T suppressor cell activity.

In APD, several organ-specific autoimmune diseases are clustered. Although APD1 is caused by loss of central tolerance, the aetiology of APD2 is multifactorial. Further evidence refers to regulatory cells, which are implicated in self-tolerance and autoimmunity. The adaptive immune system does not only consist of immune-stimulatory CD4+ helper or effector T cells and cytotoxic CD8+ T cells but is also regulated by immunosuppressive T cells. Three classes of immunosuppressive CD4+ T cells are known: induced Th3 and Tr1 cells, as well as the naturally present CD4+CD25 + FoxP3+ regulatory T cells (Treg) [17]. Treg are generated in the thymus and are present in all healthy animals and humans. Because the FOXP3-encoded scurf in protein interferes with IL-2 gene activation, Treg do not secrete IL-2 and do not proliferate upon TCR-stimulation. Treg suppress the activation of CD4+ and CD8+ cells *in vitro* and *in vivo*. They thereby prevent autoimmune disease, although the exact mechanism of suppression is unknown, and cell-contact is crucial at least *in vitro*. Depletion of Treg leads to autoimmunity in mice [18] and dysfunction of Treg has been linked to autoimmune diseases [19]. Defects in survival of suppressive function of regulatory T cells may contribute to uncontrolled expansion of auto aggressive lymphocytes. Reduced numbers of Treg and a reduction of suppressive Treg function have been reported in multiple autoimmune diseases [20–22].

In a Murine model, depletion of thymically derived CD4 (+)CD25 (+) regulatory T cells, which exert suppression in a contact-dependent manner, resulted in a syndrome, which is similar to human APD with multiple endocrinopathies [23]. It was hypothesized [19] that loss of active suppression in the periphery could be a hallmark of APD. Regulatory T cells from peripheral blood of APD, control patients with single autoimmune endocrinopathies, and normal healthy donors showed no differences in quantity, except for patients with isolated autoimmune diseases, in functionally important surface markers, or in apoptosis induced by growth factor withdrawal. Strikingly, APD regulatory T cells were defective in their suppressive capacity. The defect was persistent and not due to responder cell resistance, whereas overt quantitative or phenotypic abnormalities in regulatory T cells from these patients were not observed. In addition, samples of FOXP3 messenger RNA from APD regulatory T cells were semi-quantified and showed similar levels of FOXP3 transcripts compared with normal donor regulatory T cells despite defective suppressor function, clearly indicating that true regulatory T cells were dysfunctional. Defective regulatory T cell function in humans with APD has wide implications for

Table 2
Localization of the different autoantigen(s) and the corresponding autoimmune endocrine and non-endocrine diseases.

Disease	Autoantigen	Tissue/cells
Type 1 diabetes	GAD_{65}, IA-2, Insulin, IC, ZnT8	β-cells
Graves' disease	TSH receptor	Thyrocytes
Hashimoto's thyroiditis	TPO/Tg	Enzyme/Protein
Addison's disease	21-OH, CYP450scc	Enzyme
Hypogonadism	17-OH, CYP450scc	Leydig-/Theca cells
Hypoparathyroidism	Ca^{2+} sensitive receptor	Parathyroid
Immune gastritis	H^+, K^+-ATPase	Parietal cells
Pernicious anaemia	Intrinsic factor	Chief cells (stomach)
Celiac disease	Transglutaminase, Gliadin	Small intestine
Vitiligo	Tyrosinase	Melanocytes
Alopecia	Tyrosinhydroxylase	Hair follicles

autoimmunity in general. The results indicate that once molecular mechanisms of suppressor function are better delineated, manipulations of human regulatory T cells may eventually allow improvement of immunomodulatory strategies in diseases with impaired suppressor function. Another important category of immunosuppressive cells are the regulatory T cells Tr1/Th3, and knowledge of development and regulatory functions of such immunoregulatory cells may elucidate the aetiology for developing autoimmunity [24].

Another aspect is related to the activity of the enzyme deoxyribonuclease 1 (DNase 1). This glycoprotein is ubiquitously expressed in human tissues and plays a role in the regulation of apoptosis. It catalyses DNA hydrolysis by cleaving double-stranded DNA. The activity of this enzyme was lowered in patients with APD compared to healthy subjects [25–27]. Such a deficiency in DNase 1 may result in reduced or delayed removal of DNA from nuclear antigens and, thereby, may promote disease susceptibility to autoimmune disorders.

Environmental & genetic factors

The inheritance of APD2 is complex, with genes on chromosome 6 playing a predominant role [28–30]. In man, this chromosome contains the major histocompatibility loci. Many of the diseases of APD2 are associated with human leukocyte antigen (HLA) alleles B8 and DR3. The DR antigen has two glycoprotein chains coded for by the DR loci of chromosome 6. The alleles HLA-B8 and DR3, which are coded for by separate genes, are more often found together on the same chromosome than one would predict from their frequency in the general population. Such associations are common for alleles of different genes in the histocompatibility region (linkage disequilibrium). The allele DR3 is most closely associated with autoimmune endocrine disease. Within some families, autoimmune endocrine disease susceptibility appears to be inherited as an autosomal dominant form associated with a specific HLA haplotype. Nevertheless, family members may manifest different diseases, though the more common the disease in the general population, the higher its prevalence in affected families.

While genetic factors determine disease susceptibility, there is less than 100% concordance in monozygotic twins for the respective diseases. This suggests that other factors may be involved in disease pathogenesis. Environmental factors that can trigger DR3-associated autoimmunity include iodine and the wheat protein gliadin for celiac disease [31,32]. Thus, both genetic and environmental factors contribute to the loss of immune self-tolerance. Based on a genetic predisposition, epigenetic external factors, like viral or bacterial infections [15], and psychosocial factors might induce an autoimmune cascade [33]. Environmental factors have an important influence on the development of autoimmune diseases, but the exposure to environmental pathogens does not always lead to disease. With respect to genetics, APD2 is a polygenic disease with autosomal dominant inheritance and incomplete penetrance. In addition, familial clustering provided evidence for a genetic predisposition. APD2 is associated with HLA DR3 and DR4 antigens, and frequencies for DQA1*0301 and *0501 were increased in patients with APD2 compared to controls and monoglandular autoimmunity [12,34,35]. The genotype DR3/4, DQ2/DQ8 with DRB1*0404 is the highest HLA genotype risk for AD, either as a single disease or within APD [36]. An association of APD2 with HLA-B8 was observed in three generations of a family, whereas ten unaffected subjects did not show B8 [37]. HLA associations were described for APD component diseases T1D (DR4-DQB1*0302) and GD (B8). T1D locus 1 contains the MHC region (6p21) and, in whites revealed a positive association with HLA DRB1*04-DQA1*0301-DQB1*0302 (DR4-DQ8) or DRB1*03-DQA1*0501-DQB1*0201 (DR3-DQ2) and a negative association with DRB1*15-DQA1*0102-DQB1*0602 [38,39]. Heterozygosis for TNF*2 increased the risk for T1D in DQA1*0501-DQB1*0201/DQA1*0301-DQB1*0302 positive individuals, but this may be the result of a linkage disequilibrium with *HLA class 2 genes* [40]. A genome linkage study was performed on a data set of multiplex, multigenerational AITD families, using 387 microsatellite markers [41]. Only one locus on chromosome 6 was linked with both GD and HT. This locus was close to, but distinct from, the HLA region. Furthermore, *MHC class III genes* are associated with APD2, most specifically the gene encoding tumour necrosis factor alpha (TNF-α), a multifunctional proinflammatory cytokine, which mediates inflammatory and immune functions. Within the *TNF-α gene*, the -308*A allele of an A/G single nucleotide dimorphism occurred more frequently in patients with APD2 than in healthy controls [42].

In contrast, APD1 is a monogenic disease with autosomal recessive inheritance and is caused by mutations in the *AIRE gene* on chromosome 21 [43–45].

Diagnosis

APD2 mostly occurs in adulthood during the third and fourth decades. APD2 presenting in childhood is extremely rare; a case with hypothyroidism, followed by diabetic ketoacidosis, and AD has been reported [46]. In adults, the presence of one autoimmune endocrine disease is associated with an increased risk of developing autoimmunity to other tissues. Each of these disorders is characterized by several stages beginning with active autoimmunity and followed by metabolic abnormalities with overt disease. T1D is one of the most frequent component disorders of APD2 and is often its first symptom. At our institution, screening of 471 patients with T1D, aged 39 ± 16 years, disease duration 15 ± 10 years, showed in 127 cases (85 females) or 27% a multiple glandular involvement [47]. Additionally, 19 (4%) and eight (2%) had vitiligo and autoimmune gastritis, respectively. Subsequent screening at the Johannes Gutenberg University Medical Center of 15,000 consecutive subjects with endocrine disorders revealed a high prevalence (1%) of patients with APD2 (n = 151, 75% females, Table 3, [12]). These 151 subjects with APD2 have been followed since then. There is often a long time interval between the manifestation of the first and second component disease of APD2, which often comprises years to decades. Most frequent disease combinations are T1D/AITD (41%), followed by AITD/AD (14.6%), T1D/AITD/pernicious anaemia (5.3%), and T1D/AD (3.3%). Therefore, patients with monoglandular autoimmune disease should be serologically screened for APD2 every 2–3 years until the age of 75 years. If positive, subsequent functional screening is recommended.

The simultaneous occurrence of autoimmune hypothyroidism and T1D is often accompanied by hypoglycaemia due to decreased insulin request and increased insulin sensitivity. Hypothyroid children show growth disorders caused by chronic hypoglycaemia and decreased food intake. Substitution therapy with levothyroxine leads to increased insulin dosage. In contrast, autoimmune-induced hyperthyroidism is accompanied in 50% of the cases by glucose intolerance and in 3% by overt diabetes. Impaired glucose tolerance is due to decreased insulin sensitivity and hepatic storage of glycogen, whereas both secretion of glucagon and intestinal glucose absorption are enhanced. Similarly, concomitant presence of AD and T1D also leads to frequent hypoglycaemia due to decreased gluconeogenesis and increased insulin sensitivity.

Circulating organ-specific autoantibodies (Ab) are present in each of the component diseases of APD2 (Fig. 1). Thyrotropin receptor antibodies (TSH-R-Ab) are the hallmark of GD [48–53] and high titres of TSH-R-Ab significantly differentiate between GD phenotypes [54,55]. Furthermore, stimulatory TSH-R-Ab are a biomarker of extra thyroidal manifestations of GD, i.e. thyroid eye disease [56–60]. Occasionally, as in antigonadal- and antiadrenal-Ab, a given group of Ab will cross react with more than one gland (e.g. all steroid-producing cells). Antibodies may bind to a cell surface without functional

Table 3
Screening of 15,000 consecutive subjects with monoglandular autoimmune disease in the specialized tertiary referral endocrine outpatient clinic of the Johannes Gutenberg University Medical Center, Mainz, Germany revealed a high prevalence (1%) of patients with adult APD (n = 151, 75% females). The distribution of the various autoimmune endocrine components is shown [12].

Endocrine/non-endocrine disease	N (%)
Type 1 diabetes	92 (61%)
Graves' disease	50 (33%)
Immune thyroiditis	49 (32.5%)
Addison's disease	28 (18.5%)
Vitiligo	30 (20%)
Alopecia	9 (6%)
Primary hypogonadism	8 (5.3%)
Pernicious anaemia	8 (5.3%)

effects, or may be blocking or stimulatory [61,62]. Examples of blocking Ab include those directed at the TSH-R in patients with AITD [63–65]. Other Ab such as anti-thyroperoxidase and antiparietal cell Ab are prevalent in healthy relatives of patients with APD. The presence of such Ab may precede clinical disease by many years, but in contrast to anti-islet Ab, anti-thyroid Ab can be present for decades without progression to overt disease.

Antibodies against steroidal enzymes (e.g. 21-hydroxylase) are of high prognostic value [66] and will help identify patients at risk for developing AD [67]. This might prevent delayed diagnosis of adrenal failure. With respect to T1D, it has been demonstrated that antiidiotope reagents were able to distinguish between childhood-onset T1D and adult-onset T1D with polyendocrine susceptibility [68]. Childhood-onset T1D-IAA differed from adult-onset T1D-IAA in their specificity for human insulin and from their antiidiotope amino acid sequence. Based on improved immunogenic understanding and Ab screening assays, T1D is now predictable [14].

At our institution, the Ab profile in patients with APD2, patients with monoglandular and non-glandular autoimmune diseases (MGA2), patients with monoglandular autoimmunity (MGA), subjects with non-glandular autoimmunity (NGA), and clinically healthy relatives had been analysed. Subjects were screened for Ab against alpha-fodrin-IgA/IgG, SS-A/SS-B, thyroid peroxidase (TPO), gliadin-IgA/IgG, transglutaminase IgA/IgG, ASCA-IgA/IgG, antinuclear Ab, and anti-neutrophil cytoplasm Ab using ELISA and/or radioimmunoassay. Overall Ab prevalence in patients with APD2, MGA2, relatives with MGA, NGA, and healthy relatives was 92%, 87%, 79%, 67%, and 56%, respectively. Prevalence for anti-TPO-Ab was different between APD2, MGA2, MGA, NGA, and healthy relatives amounting 50%, 54%, 50%, 13%, and 12%, respectively, (chi-square = 37.6, $p < 0.0001$). Also, prevalence of glutamic acid decarboxylase (GAD) Ab was increased in patients with APD2, compared to healthy persons [47]. There were no statistically significant group differences with respect to the other Ab. In summary, silent Ab were highly prevalent in families with APD2, and the prevalence of these Ab was associated with the number of involved glands. Thus, these Ab may be predictive for the development of future autoimmune endocrine diseases.

Testing & treatment

Approximately one in five first-degree relatives of patients with APD2 has an unrecognized endocrine disorder, usually the relatively common autoimmune HT, and we recommend routine screening of thyroid function in this high-risk population. In contrast and most specifically, in subjects with either monoglandular T1D or AD, organ-specific Ab screening and functional testing will help

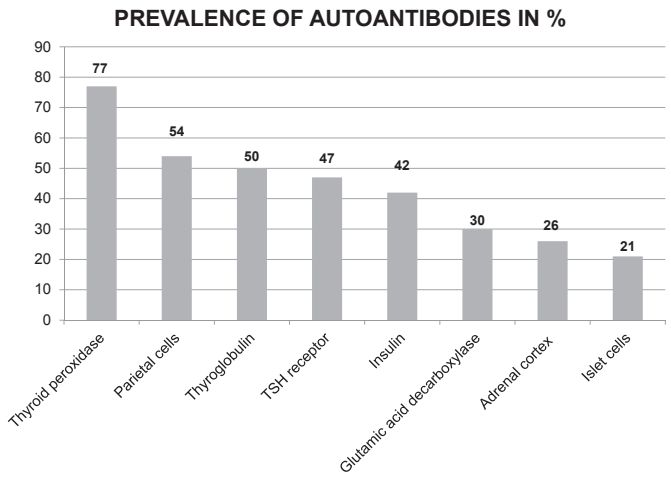

Fig. 1. Prevalence of frequent organ-specific autoantibodies in adult patients with APD [12].

identify both patients at risk for developing APD2 as well as an already present subclinical APD. In the presence of a patient with clinical and biochemical signs of primary AD, the determination of 21OH-Ab enables the unequivocal demonstration of the autoimmune origin of the disease. In subjects with AD, screening for other endocrine disorders is required, given the frequent association of autoimmune adrenal insufficiency with AITD, T1D or other immune-mediated diseases. Thus, in any patient with AD, determination of thyroid peroxidase-, thyroglobulin-, GAD 65, and islet Ab should be performed and if negative, repeated every few years. Since most APD2 patients are adults, determination of insulin- or IA2-Ab is not strictly necessary, given the low diagnostic sensitivity of these markers for adult-onset T1D. In the case of positivity for GAD65-and islet cell-Ab, an oral glucose tolerance is needed to demonstrate a glucose intolerance not revealed by fasting blood glucose. Although T1D develops frequently before AD, GAD65-Ab are detected in 5–7% AD patients without T1D and a proper follow-up should be performed in islet cell-Ab positive patients. The determination of 17OH- and P450scc-Ab will enable the identification of subjects at high risk for primary hypogonadism, with a high positive predictive value in women. Furthermore, determination of transglutaminase-Ab [4,5,31,32] could be included in the screening of children with T1D. In addition, determination of 21OH-Ab should be performed in all patients with T1D and AITD, as the identification of subjects positive for adrenal-Ab is highly predictive for future adrenal insufficiency [66]. In subjects with 21OH-Ab and normal cortisol levels, an ACTH stimulation test will enable the identification of subjects with pre-clinical adrenal dysfunction. Subjects with normal cortisol response could simply be followed-up, with re-evaluation of adrenal-Ab levels, basal and ACTH-stimulated cortisol on a yearly basis.

Many of the endocrine disorders of APD are adequately treated with hormonal replacement therapy if the disease is recognized early (Fig. 2). Subjects with pathological ACTH test and increased levels of basal plasma ACTH require close clinical follow-up with repetition of the test every 6 months. A replacement therapy with hydrocortisone or cortisone acetate should be considered in the case of undercurrent stressful events. Hypoglycaemic episodes and a decreasing insulin requirement in T1D can be one of the earliest signs of the development of adrenal failure [9,69]. Replacement of levothyroxine without simultaneous adrenal steroid replacement in a hypothyroid patient with AD can precipitate an adrenal crisis [70]. Replacement of thyroxine increases the cortisol turnover rate in the liver, and this may tax a failing adrenal gland.

Psychosocial morbidity & family clustering

Patients with APD are exposed to many limitations of their illness in daily life and their routine duties and daily affairs can be impaired. Further, patients with APD rely on a lifelong daily treatment, including hormonal replacement therapy depending on the specific organ failure. To objectify the degree of physical and emotional distress, the psychometric profile of these patients was prospectively evaluated [71]. Subsequent to a complete endocrine investigation, three international validated self-assessment questionnaires were applied in patients with APD2: the Medical Outcome Health Survey Short Form-36 (MOS SF-36), the Giessen Complaint List (GBB-24) and the Hospital Anxiety and Depression Scale (HADS). Further, the level of physical and emotional distress, the health-related quality of life (HRQOL) and the somatic complaints were evaluated in patients with APD. Every scale of the SF-36, GBB-24, and the HADS anxiety score demonstrated markedly impaired physical and emotional well-being, foremost in female subjects ($p < 0.001$). Compared to a German reference cohort, all subscales of the SF-36 were decreased ($p < 0.001$). Sex-and age-matched z-scores were significantly lower for physical functioning, physical role limitations, bodily pain, general health perception, vitality, social functioning, emotional role limitations and mental health. In addition, the global score of discomfort was increased in comparison to the reference population ($p < 0.001$). Generalized anxiety (25%, $p < 0.001$) and depression episode (18%, $p < 0.001$) were prevalent in APD. Neither time interval between two endocrine diseases, duration of APD, age, nor autoantibody presence influenced psychometric testing results.

A prospective and controlled study was performed to collect data pertaining to familial clustering [10]. The risk for developing AITD was 16-fold and 15-fold increased in children and siblings, respectively, of patients with AITD and/or APD. In particular, children and siblings of index cases with HT had a 32-fold and 21-fold increased risk, respectively, for developing immune thyroiditis. In comparison,

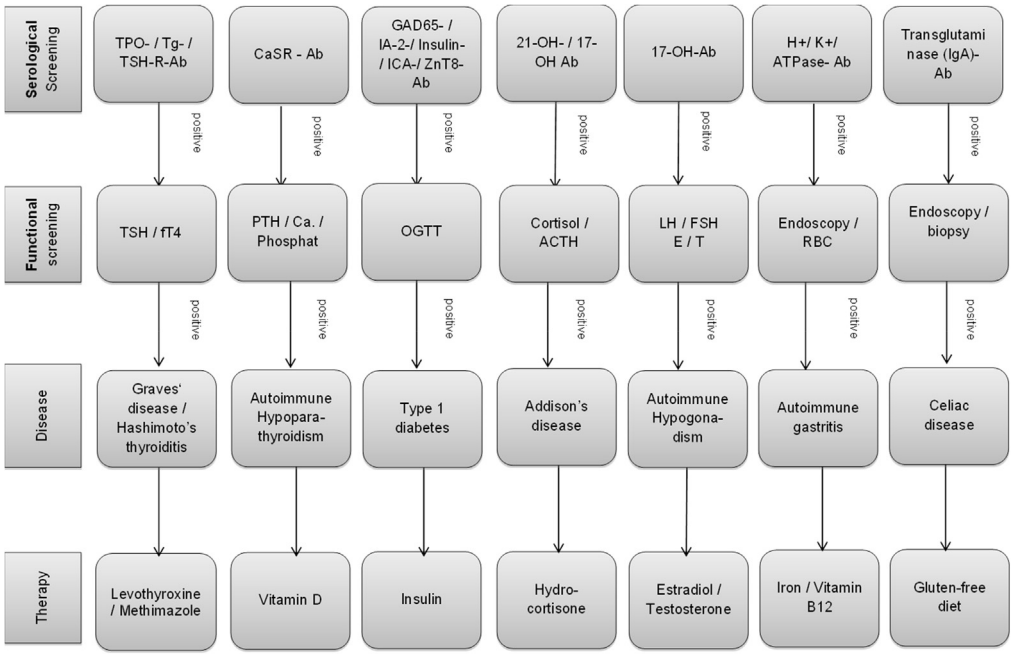

Fig. 2. Serologic and functional screening for associated glandular and non-glandular autoimmune disorders in patients with autoimmune polyglandular disease. Ab: Antibody; OGTT: oral glucose tolerance test; ACTH: Adrenocorticotropic hormone; CaSr: Calcium-sensing receptor; E: Estradiol; FSH: Follicle-stimulating hormone; fT4: Free thyroxine; GAD65: Glutamate decarboxylase; IA-2: insulinoma antigen 2; ICA: islet cell cytoplasm; LH: Luteinizing hormone; PC: Parietal cell; PTH: Parathyroid hormone; RBC: Red blood cell count; T: total testosterone; Tg: Thyroglobulin; TPO: Thyroid peroxidase; TSH-R: TSH receptor; TSH: Thyrotropin; ZnT8: Zinc Transporter-8; 17-OH: 17-hydroxylase; 21-OH: 21-hydroxylase.

the risk for developing GD was enhanced 7-fold in both children and siblings. The high prevalence of AITD in first degree, foremost female relatives of patients with AITD and/or APD demonstrates the importance of family history for developing AITD. Hence, regular screening of children and siblings of patients with APD and AITD for presence of HT or APD is recommended. In another study, clinical and serological evaluation of consecutively recruited patients with APD and their representative kindred and siblings was done [11]. Patients and relatives answered the three validated questionnaires for psychosocial evaluation (SF-36, HADS and GBB). More than half of the first-degree relatives (52%) had an autoimmune disease whereas HT and autoimmune type-A gastritis were the most prevalent endocrine and non-endocrine components. Thyroid peroxidase autoantibodies were most prevalent in involved relatives. Compared to a German reference group, all scales of the SF-36 were markedly decreased in involved relatives ($p < 0.001$). Anxiety and depression scales were pathologically increased in relatives ($p < 0.001$). In addition, all GBB scales were elevated for relatives ($p < 0.001$). Patients with both glandular and non-glandular autoimmune diseases showed the most pathological psychosocial results. Thus, familial clustering is high in patients with APD.

In conclusion, patients with APD have a severely impaired psychometric profile. Quality of life and psychosocial status are poor in both patients and involved relatives. Multidisciplinary management of these multiplex families in specialized centers is warranted.

Perspective

In APD, genetic associations with HLA haplotypes and polymorphisms of genes encoding immunologically relevant gene products have been reported [28,72–74]. The associations of autoimmune endocrinopathies with polymorphisms of these particular genes support the hypotheses that they may

function to influence general predisposition, increase susceptibility, or influence the clinical presentation of autoimmune diseases. Other factors such as environmental triggers and yet unidentified genetic loci may modulate disease or target tissue phenotype. Therefore, future research is required to identify the other players in the process of regulating immune tolerance and the process of defining the tissue targets of autoimmune diseases. Since actual immunogenic data are scarce, further studies are necessary to elucidate the specific and general immunologic mechanisms, which underlie the development of APD. Nowadays, genetic screening is useful and required for the monogenic APD1, but not strictly for the polygenic type 2. Continuing research is warranted to further clarify the genetic background of APD, to identify susceptibility genes, and to understand their interactions. Additional knowledge regarding these genes will allow genetic screening of patients at risk. Advances in genetics and pathogenesis of APD and its component diseases may be valuable in the prevention of morbidity and mortality of the subjects involved. Future research should also focus on family studies with a large number of samples from different population groups. This might offer further knowledge on the inheritance of APD as well as on the familial risk to develop APD.

Summary

APD are based on the presence of lymphocyte infiltration in the affected gland, organ specific antibodies in the serum, cellular immune defects, and an association with the *HLA DR/DQ genes* or immune response genes. Autoantibodies to the various endocrine and non-endocrine tissues not only offer a diagnostic clue to the autoimmune nature of diseases but also can be used to identify asymptomatic individuals who are at risk of developing other component diseases of the syndrome. Although target tissues or glands differ, several common threads link the APD. The autoimmune destruction of most target glands appears to be a slow process with a long preclinical prodromal that may last for years. During this period, autoantibodies, lymphocyte abnormalities, and subclinical endocrine defects are usually present. As knowledge of target antigens has progressed, it appears that despite polyendocrine disease, within each gland specific antigens are the targets of the autoimmune process. A defect resides in one of the genes of the HLA locus that, in concert with other gene(s), results in susceptibility. Genetic susceptibility is necessary but not sufficient to produce the disorder. This is illustrated by the lack of 100% concordance of disease in identical twins.

Practice points

- Autoimmune polyglandular diseases encompass at least two autoimmune-induced endocrine disorders
- Time interval between first and second endocrine component is largely variable
- Psychosocial morbidity is present
- Involvement of first-degree relatives is very prevalent
- Long-term follow up of patients and first degree relatives is recommended
- Serological screening is recommended in patients with monoglandular autoimmune disease. If positive, functional screening should follow

Research agenda

- Elucidate specific and general immunologic mechanisms, which underlie development of APD.
- Clarify genetic background of APD
- Identify susceptibility genes
- Understand interactions of above genes

Disclosure

The authors have nothing to disclose.

Declaration of Competing Interest

Both authors have nothing to disclose and had no sources of funding.

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