Polyglandular Autoimmune Syndrome Type II

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Summary

The polyglandular autoimmune syndromes (PAS) comprise a wide spectrum of autoimmune disorders. There exist a juvenile (PAS I) and an adult type (PAS II). The nature of PAS has been 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 human leucocyte antigen (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 diseases of PAS. A defect resides in one of the genes of the HLA locus which, 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. Genetic testing may identify patients with PAS I, but not those with PAS II. For PAS II, susceptibility genes are known which increase the risk for developing autoimmune disorders, but must not be causative. These are certain HLA genes, the cytotoxic T-lymphocyte antigen (CTLA-4) gene, and the protein tyrosine phosphatase non-receptor type 22 (PTPN22) genes on chromosomes 6, 2, and 1, respectively. When the genetic defects and environmental influences of organ-specific autoimmunity are better understood, it may be possible to devise specific replacement or corrective therapies. Given the similar features of many of the organ-specific autoimmune disorders, it is likely that if immunotherapeutic modalities are successful in one disease, they may be of benefit in related disorders.

Definition and prevalence

The polyglandular autoimmune syndromes (PAS) define the autoimmune induced failure of at least two glands. They comprise a wide spectrum of autoimmune disorders [1,2] and encompass a rare juvenile type PAS I and a more frequent adult type PAS II/III [3]. Contrary to PAS I, PAS II/III primarily manifest in adult age. PAS II is defined as the association between autoimmune Addison’s disease and either autoimmune thyroid disease or type 1 diabetes, or both [4,6].
PAS III is defined by the presence of autoimmune thyroid disease and autoimmune disorders other than Addison’s disease and hypoparathyroidism, e.g. type 1 diabetes [7,8]. In contrast to PAS I, chronic candidiasis is not present in PAS II/III. Further autoimmune endocrine and non-endocrine component disorders may be manifest in PAS II/III. Due to the tremendous overlap of phenotypes in PAS II/III, for daily use, it is clinically relevant to differentiate the more common adult type encompassing both PAS II/III from the rare juvenile type PAS I [9,10]. The adult type PAS II/III is more common than PAS I, but still is a rare syndrome. Its prevalence is 1:20,000 [11]. It occurs more frequently in women. The male-to-female ratio is 1:3. The incidence of this syndrome peaks at ages 20 to 60 years, mostly in the third or fourth decade.

### Clinical spectrum

PAS II is characterized by the presence of autoimmune adrenalitis (Addison’s disease) and at least one other autoimmune disorder [3,4]. The second disease component may be either autoimmune thyroid disease (AITD) or type 1 diabetes or both [2,6]. Further endocrine (hypogonadism, hypoparathyroidism,) and non-endocrine component diseases (autoimmune gastritis, pernicious anaemia, vitiligo, autoimmune hepatitis and myasthenia gravis) may be present [5,7]. The associated minor autoimmune diseases are less frequent than in PAS I. PAS II mostly occurs in adulthood during the third and fourth decades. About half of patients with PAS II present initially type 1 diabetes [12]. These patients may develop PAS II in the future. In adults, the manifestation of one autoimmune endocrine disorder increases the risk of developing other autoimmune disorders. Many years may separate the onset of different component diseases [13]. All diseases resulting in autoimmune tissue destruction appear to have a prolonged phase of cellular loss preceding overt autoimmune glandular disease. Silent autoantibodies are prevalent in families with PAS II. Therefore, antibody screening may be predictive for the development of future autoimmune endocrine diseases. Annual screening of ACTH is recommended for such patients. PAS III is defined by the presence of AITD and autoimmune disorders other than Addison’s disease and hypoparathyroidism [7]. Endocrine and non-endocrine component diseases include type 1 diabetes, chronic autoimmune gastritis, pernicious anaemia, vitiligo, and alopecia. Further component disorders may be myasthenia gravis, hypogonadism, Sjögren syndrome, systemic lupus erythematosus, and rheumatoid arthritis. Most frequently observed disease combination is between AITD and type 1 diabetes. AITD peaks in the fourth decade (Graves ‘disease) or fifth and sixth decade (Hashimoto’s thyroiditis). The simultaneous occurrence of hypothyroidism and type 1 diabetes is often accompanied by hypoglycaemia due to decreased insulin request and increased insulin sensitivity. Glucose intolerance accompanies hyperthyroidism in 50% of patients.

### Table I

<table>
<thead>
<tr>
<th>Disease</th>
<th>Autoantigen</th>
<th>Tissue/Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves disease</td>
<td>TSH receptor</td>
<td>Thyrocytes</td>
</tr>
<tr>
<td>Hashimoto’s thyroiditis</td>
<td>TPO/Tg</td>
<td>Enzyme/Protein</td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Ca²⁺ sensitive receptor</td>
<td>Parathyroid</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>GAD65, IA-2, Insulin</td>
<td>β-cells</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>21-OH, 17-OH, P450scc</td>
<td>Enzyme</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>17-OH, CYP450scx</td>
<td>Leydig/Theca cells</td>
</tr>
<tr>
<td>Autoimmune gastritis</td>
<td>H⁺, K⁺-ATPase</td>
<td>Gastric parietal cells</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>Intrinsic factor</td>
<td>Gastric chief cells</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>Transglutaminase</td>
<td>Small intestine</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Tyrosinase</td>
<td>Melanocytes</td>
</tr>
<tr>
<td>Alopecia areata</td>
<td>Tyrosinhydroxylase</td>
<td>Hair follicles</td>
</tr>
</tbody>
</table>

TPO: thyroid peroxidase; Tg: thyroglobulin; GAD: glutamate decarboxylase; 21-OH: 21 Hydroxylase; P450scc: steroid cleavage cells.

In contrast to patients with PAS I, patients with PAS II/III do not develop mucocutaneous candidiasis. Also, hypoparathyroidism is very rare in PAS II/III. Hypoparathyroidism in childhood is indicative of PAS I. In PAS II/III, circulating organ-specific autoantibodies are present in each of the component diseases. Occasionnally, antibodies will cross-react with more than one gland (e.g. steroid-producing cells). Antithyroid peroxidase and antiparietal cell antibodies are prevalent in healthy relatives of patients. Antibodies may precede clinical disease by many years, but in contrast to anti-islet antibodies, anti-thyroid antibodies can be present for decades without progression to overt disease. Antibodies against steroidal enzymes (e.g. 21-hydroxylase) are of high prognostic value. They will aid to identify patients at risk for developing Addison’s disease [14,15] (tables I-III).

### Immunogenetics

In contrast to PAS I, PAS II/III are genetically complex and multifactorial syndromes. Several genetic loci possibly interact with environmental factors. Other than PAS I, PAS II/III are strongly associated with certain alleles of the human leucocyte antigen (HLA) genes within the major histocompatibility complex. PAS II frequently clusters in families. Several generations are often affected by one or more component diseases [1]. The inheritance pattern seems to be autosomal-dominant with incomplete penetrance in some patients [5]. Two genes have been shown to be associated with PAS II. These are human leucocyte antigen (HLA) genes on chromosome 6 and the
cytotoxic T-lymphocyte antigen (CTLA-4) gene on chromosome 2 (location: 2q33). Of these, HLA appears to have the strongest gene effect [4]. Many PAS II component disorders are associated with an increased frequency of the HLA haplotype A1, B8, DR3, DQA1*0501, DQB1*0201 [16]. Addison’s disease is strongly associated with DR3 and DR4 [17]; the observed relative risks are 6.0, 4.6, and 26.5 for DR3, DR4, and DR3/DR4, respectively. Addison’s disease is also correlated with DQ2/DQ8 with DRB1*0404, both as a single disease as well as within APS2 [18]. Type 1 diabetes is positively associated with DR4-DQB1*0302, DRB1*04-DQA1*0301-DQB1*0302 or DRB1*03-DQA1*0501-DQB1*0201 (DR3-DQ2), and negatively associated with DRB1*15-DQA1*0102-DQB1*0602 [19,20]. In PAS II patients without islet cell autoimmunity, only the haplotype DR3-DQB1*0201 occurred more frequently [16]. The DRB1*04-DQB1*0301 haplotype increases the risk of developing Hashimoto’s thyroiditis [21]. The CTLA-4 gene is assigned to chromosome 2 (location: 2q33). It comprises four exons and encodes a protein which acts as an important modifier of T-cell activation with down-regulatory properties. An A49G substitution in exon 1 of the CTLA-4 gene with more G alleles has been associated with Graves’ disease in Caucasians and Asians [22–27] and with Hashimoto’s thyroiditis [28]. With respect to Graves’ disease, family studies give evidence for an increased transmission of the G allele from heterozygous parents to affected offspring compared to unaffected offspring [29]. A 3’ microsatellite (AT)n, repeat of the CTLA-4 gene may also be important. The 106 bp allele of the AT repeat was more frequently observed in Caucasian patients with GD than in healthy controls [26]. CTLA-4 alleles have been mainly linked to AITD (Graves’ disease and Hashimoto’s thyroiditis), and to a weaker extent to type 1 diabetes. Addison’s disease was also associated with CTLA-4 alleles, particularly in a subgroup showing HLA-DQA1*0501. Data indicate interactions between HLA and CTLA-4 genes, further unidentified genes and environmental factors.

PAS III is also characterized by a complex inheritance pattern. With respect to the combination of type 1 diabetes and AITD, at least three genes are involved as major susceptibility genes: HLA class II, CTLA-4, and PTPN22. HLA class II is a potential gene locus for combined susceptibility to type 1 diabetes and AITD as has been shown in Caucasians and Asians [16,30–35]. Most family studies give evidence that the haplotype HLA-DR3-DQB1*0201 is the primary haplotype conferring susceptibility to both type 1 diabetes and AITD within families [34]. Here, DR3 seems to be the primary allele conferring risk to both type 1 diabetes and AITD, whereas DQB1*0201 seems to be of secondary significance [34]. Many population studies indicate that both HLA haplotypes DR3-DQB1*0201 and DR4-DQB1*0302 contribute to the A53 variant of combined type 1 diabetes and AITD [16,34,36,37]. The gene products of the HLA class II genes are involved in immune reactions. The different HLA class II alleles are characterized by different affinities for peptides. As a consequence, some autoantigenic peptides may be recognized by T-lymphocyte receptors, whereas others may not [38]. The causative CTLA-4 gene polymorphism for autoimmunity may be located in the 3’UTR (untranslated region) of the CTLA-4 gene [39]. Here, a (AT)n microsatellite polymorphism occurs with longer and shorter repeats of AT. The longer repeats are associated with decreased inhibitory function of CTLA-4 [40]. Longer repeats were correlated with a shorter half-life of the CTLA-4 mRNA than shorter repeats [41]. Further candidate polymorphisms may be also affect disease, to be investigated.

### Table II

<table>
<thead>
<tr>
<th>Disease</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 diabetes</td>
<td>92 (61)</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>50 (33)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>49 (32.5)</td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>28 (18.5)</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>8 (5.3)</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Pernicious anaemia</td>
<td>8 (5.3)</td>
</tr>
</tbody>
</table>

**Polyglandular Autoimmune Syndrome Type II**

**Table II**

| Screening of 15,000 consecutive subjects with autoimmune monoglandular disease in the endocrine outpatient clinic of the Gutenberg University Medical Center revealed a high prevalence (1%) of patients with the adult PAS type II/III (n = 151, 75% females). The distribution of the various autoimmune endocrine diseases is shown in reference [13].

<table>
<thead>
<tr>
<th>Autoantibodies against</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid peroxidase</td>
<td>77.2</td>
</tr>
<tr>
<td>Thyroglobulin</td>
<td>49.5</td>
</tr>
<tr>
<td>TSH receptor</td>
<td>46.7</td>
</tr>
<tr>
<td>Insulin</td>
<td>41.8</td>
</tr>
<tr>
<td>Glutamic acid decarboxylase</td>
<td>30.3</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>26.3</td>
</tr>
<tr>
<td>Islet cells</td>
<td>21.1</td>
</tr>
<tr>
<td>Gastric parietal cells</td>
<td>53.9</td>
</tr>
</tbody>
</table>

According to reference [13].

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in future studies. The *CTLA-4* gene encodes a negative regulator of T-cell activation which is expressed on the surface of activated T-lymphocytes. It is involved in the interaction between T-lymphocytes and antigen presenting cells (APCs) [42]. APCs present to the T-lymphocyte receptor an antigenic peptide bound to an *HLA* class II protein on the cell surface. By this way, APCs activate T-lymphocytes. For T-lymphocyte activation, a co-stimulatory signal is necessary which is given by APCs or other cells. Co-stimulatory signals on the surface of APCs interact with receptors (e.g. *CTLA-4*) on the surface of CD4+ T-lymphocytes during antigen presentation [42]. *CTLA-4* down regulates T-lymphocyte activation [43]. *CTLA-4* polymorphisms are associated with several autoimmune disorders e.g. AITD and Addison’ disease [44,45]. By contrast, findings are inconsistent with respect to the association of *CTLA-4* and type 1 diabetes, suggesting only a weak effect [22,39,45–47]. A 3’UTR (AT)n, microsatellite polymorphism with longer and shorter repeats of AT may be related to autoimmunity. The longer repeats are associated with decreased inhibitory function of *CTLA-4* [40]. Longer repeats were correlated with a shorter half-life of the *CTLA-4* mRNA than shorter repeats [41]. The *CTLA-4* AT repeat affects the inhibitory function of *CTLA-4* in that the long AT repeat allele is associated with a reduced control of T-cell proliferation in patients with Graves’ disease [40]. The protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene maps on chromosome 1 (location: 1p13) [48]. This gene encodes the lymphoid tyrosine phosphatase (LYP) protein. Alternative splicing of this gene results in two transcript variants encoding distinct isoforms of the protein. A single nucleotide polymorphism (SNP) in the *PTPN22* gene, an 1858C→T transition, results in an arg620-to-trp (R620 W) substitution in the LYP protein [49]. The minor t allele was found to be associated with type 1 diabetes [49], AITD [50] and other autoimmune diseases. This is involved in altered T-lymphocyte activation. In Asian patients, a novel SNP in the promoter region of the *PTPN22* gene, G1123 C, has been recently identified and associated with type 1 diabetes and AITD [51]. Therefore, the promoter SNP is a further possible causative variant for autoimmunity. Additional candidate polymorphisms may be also causative [52]. The *PTPN22* gene encodes the lymphoid tyrosine phosphatase (LYP) which is expressed primarily in lymphoid tissues. It is expressed in both immature and mature B and T-lymphocytes. This enzyme associates with the molecular adapter protein CBL and may be involved in regulating CBL function in the T-cell receptor signalling pathway. LYP inhibits the T-lymphocyte antigen receptor signalling pathway [53]. It binds to the protein kinase (Csk), thereby limiting the response to antigens [54]. A mutation in *PTPN22* causing a tryptophan for arginine substitution in the LYP protein (R620 W) has been reported to be associated with autoimmune disorders including type 1 diabetes, AITD and vitiligo [44,54–56]. By contrast, Addison’s disease is not associated with *PTPN22* [56]. With respect to AITD, the *PTPN22* variant is associated with Graves’ disease as well as with Hashimoto’s thyroiditis [25,50,57]. The association with Graves’ disease seems to be stronger than with Hashimoto’s thyroiditis.

**Pathogenesis**

Auto-aggression in PAS type II/III is considered multifactorial. The principal antigen-specific immune response is initiated by antigen presenting cells [58]. Ubiquitous dendritic cells are the most important antigen presenting cells. Immature dendritic cells pick up antigen molecules in non-lymphoid organs, fragment the antigens, and migrate to the secondary lymphoid organs presenting their *HLA* class I or II associated antigen fragments. This activates antigen-specific T helper cells that stimulate by use of different cytokines the cellular immune response via cytotoxic T-lymphocytes (Th1) and/or the humoral immune response via B-lymphocytes (Th2). During the Th1 response, activation of mononuclear phagocytes also occurs, because Th1 cytokines comprise proinflammatory mediators. T-suppressor cells regulate the immune responses; when immune tolerance is lost, auto-aggression occurs. A T-cell population (CD4 + CD25 + ) with potent regulatory properties that inhibit the activation of CD4 + CD25– T effector cells has been described [59,60]. These T-cells regulate auto aggressive T- and B-cells and may have profound influence on the control of human autoimmune diseases.

Animal models of the pathogenesis of PAS II/III are consistent with a viral infection theory as well as a suppressor effect theory. The viral infection-theory couples autoimmunity disease with viral infection. The so-called “molecular mimicry” is characterized by an immune response to an environmental agent that cross-reacts with a host antigen, resulting in disease. In an animal model, mice infected with reovirus type 1 developed PAS [61,62]. Some of the resultant autoantibodies showed cross-species reactivity, recognizing similar antigenic determinants in mouse and human organs. With respect to the suppressor effect theory, administration of the immunosuppressive drug cyclosporine to new-born BALB/c mice caused a selective defect of the regulatory T suppressor cells [63]. Thymectomy conserved the T-cell defect and produced autoimmune diseases in a wide spectrum of organs (thyroiditis, insulinitis, adrenalitis, oophoritis/orchitis, and gastritis) with pathology similar to that of human organ-specific immune diseases. These pathological processes lead to the preclinical phase of PAS, with production of organ-specific antibodies and progressive immune-mediated destruction of endocrine tissues. In the clinical phase, major organ destruction occurs due to the autoimmune activity that is primarily characterized by chronic inflammatory infiltration of lymphocytes. Destruction of endocrine glands causes their secretory insufficiency. The role of apoptosis in immunodestruction has been associated with deregulation of apoptotic signalling pathways.
Dysfunction of the Fas apoptotic pathway or production of soluble factors including soluble Fas and soluble Fas ligand may be involved in the pathogenesis of endocrine diseases. In the case of type 1 diabetes it has been postulated that increased susceptibility of islet cells to the induction of apoptosis by cytotoxic T-cells – presumably through the cell surface receptor Fas pathway – may be responsible for facilitated death of islet β-cells [3,6].

**Management**

Many of the endocrine disorders of the PAS II/III are adequately treated with hormonal replacement therapy if the disease is recognized early [64]. 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 a type 1 diabetic can be one of the earliest signs of the development of adrenal failure. Replacement of levothyroxine without simultaneous adrenal steroid replacement in a hypothyroid patient with Addison’s disease can precipitate an adrenal crisis. Replacement of thyroxin increases the cortisol turnover rate in the liver, and this may tax a failing adrenal gland. Psychometric testing of patients with the adult PAS type II and/or III may be markedly impaired as recently shown [65] and psychological counselling of the patients with this complex chronic autoimmune disorder might be warranted.

Approximately one in seven first degree relatives of patients with PAS II/III have an unrecognized endocrine disorder, usually the relatively common autoimmune thyroiditis [66], and we recommend routine screening of thyroid function in this high risk population [64–66]. In contrast and most specifically, in subjects with either monoglandular type 1 diabetes or the relatively rare autoimmune adrenal failure, organ-specific autoantibody screening and functional testing will help identify both patients at risk for developing PAS II as well as an already present subclinical polyglandular syndrome. In the presence of a patient with clinical and biochemical signs of primary adrenal failure, the determination of 21-OH antibodies enables the unequivocal demonstration of the autoimmune origin of the disease. In subjects with autoimmune Addison’s disease, screening for other endocrine disorders is required, given the frequent association of autoimmune adrenal insufficiency with thyroid diseases, type 1 diabetes or other immune-mediated diseases. Thus, in any patient with Addison’s, determination of thyroid peroxidase-, thyroglobulin-, Glutamate decarboxylase (GAD65), and islet antibodies should be performed and if negative, repeated every few years. Since most PAS II patients are adults, determination of insulin or IA2 antibodies is not strictly necessary, given the low diagnostic sensitivity of these markers for adult-onset type 1 diabetes. In the case of positivity for GAD65 and islet cell antibodies, an oral glucose tolerance is needed to demonstrate a glucose intolerance not revealed by fasting blood glucose. Although type 1 diabetes develops frequently before Addison’s disease, GAD65 antibodies are detected in 5 to 7% Addison patients without type 1 diabetes and a proper follow-up should be performed in islet cell antibody positive patients. The determination of 17 hydroxylase and P450scs antibodies will enable the identification of subjects at high risk for primary hypogonadism, with a high positive predictive value in women. Furthermore, determination of transglutaminase antibodies could be included in the screening of PAS children with type 1 diabetes. Also, determination of 21 hydroxylase (21-OH) antibodies should be performed in all patients with type 1 diabetes and thyroid autoimmune diseases, as the identification of subjects positive for adrenal autoantibodies is highly predictive for future adrenal insufficiency. In subjects with 21-OH antibodies and normal cortisol levels, an ACTH stimulation test, will enable the identification of subjects with preclinical adrenal dysfunction. Subjects with normal cortisol response could simply be followed-up, with re-evaluation of adrenal antibody levels, basal and ACTH-stimulated cortisol on a yearly basis. Further serological and functional testing includes autoantibodies against calcium sensing receptor for early testing of autoimmune induced hypoparathyroidism. Definitive diagnosis of glandular failure is obtained by measurement of gonadotropins, male (testosterone) or female (estradiol) hormones, baseline cortisol, parathormone, and finally the serum electrolyte (box 1).

**Box 1**

**Diagnostic screening investigation for PAS type II/III**

**Functional testing**

- TSH, FSH, LH, fT3, testosterone, estriadiol, glucose, fasting morning cortisol
- ACTH stimulation test (when adrenal antibodies are present)
- Serum Na+, K+, Ca++, blood cell count

**Autoantibodies to**

- Islet cells, GAD, (optional IA2)
- TPO, TSH receptor
- Cytochrome P450 enzymes (especially 21-Hydroxylase)
- H⁺K⁺-ATPase of the parietal cells, intrinsic factor
- Transglutaminase, (optional gliadin)

**Molecular analysis**

- AIRE gene for PAS type I, only
- HLA-typing and subtyping (optional and for scientific purpose)
- AIRE gene, autoimmune regulator gene; GAD, glutamic acid decarboxylase; IA2, protein tyrosine phosphatase; TPO, thyroid peroxidase
Each of the component disorders is characterized by several stages beginning with active autoimmunity and followed by metabolic abnormalities with overt disease. Circulating organ-specific autoantibodies are observed in the various component diseases of PAS II/III. The presence of such antibodies may precede clinical disease by many years. Therefore, such antibodies may be predictive for the development of future autoimmune polyglandular diseases and relatives of affected patients should be regularly screened. Several endocrine component disorders can be adequately treated with hormonal replacement therapy if the disease is recognized early. Regular follow-up of patients with monoglandular autoimmune disease, most especially those with Addison’s disease, type 1 diabetes, and to a lesser degree Hashimoto’s thyroiditis is warranted, since a second autoimmune glandular disease may occur between one and twenty years after the manifestation of the first glandular failure. Furthermore, serological screening of the first-degree relatives of patients with PAS II/III is recommended due to the high prevalence of various autoantibodies in these kindred’s. Presence of organ autoantibodies in these relatives should be completed by functional diagnosis of an eventual glandular dysfunction. Genetic testing may identify patients with PAS I, but not those with PAS II/III. For PAS II/III, only susceptibility genes might be identified which increase the risk for developing autoimmune diseases, but must not be causative for the disease [67,68]. HLA-typing is optional and may be performed in specialized centers in first-degree relatives of patients with PAS and/or multiplex families (box 1). Therefore, the following exposition is restricted to genetic testing for PAS I. For the adult PAS type II/III, genetic counselling is rather optional since the adult type is caused polygenic and multifactorial. Several genes as well as environmental factors may be involved in the pathogenesis, contributing to the loss of immune self-tolerance. Based on a genetic predisposition, external factors as pathogens, viral or bacterial infections, and psychosocial factors might induce autoimmune reactions [69]. Counselling of the adult type should emphasize the rationale for a regular follow-up of the kindred’s and first-degree relatives of these patients.

Concluding remarks

With respect to the significant morbidity and potential mortality of the disease, the main diagnostic objective is to detect PAS Type II/III at an early stage, with the advantage of less frequent complications, effective therapy and better prognosis. This requires that patients at risk (first-degree relatives of patients with PAS II/III and family members or kindred of multiplex families with autoimmune endocrine diseases) be regularly screened for subclinical autoimmunopathies before clinical manifestation will occur. Regarding the possible large time interval between manifestation of the first and further autoimmune endocrinopathies, regular and long-term follow-up of patients with endocrine autoimmune disorders is warranted. Considering the high incidence of one or more endocrinopathies in first-degree relatives of patients with PAS II/III, family members of patients should be regularly screened, because they may develop autoimmune endocrinopathies in the future.

Disclosure of interest: The author declares that he has no conflicts of interest concerning this article.

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Polyglandular Autoimmune Syndrome Type II

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