Polyglandular Autoimmune Syndrome Type I

Emmanuelle Proust-Lemoine1,2, Pascale Saugier-Veber3, Jean-Louis Wémeau1

1. CHRU de Lille, hôpital Claude-Huriez, clinique endocrinologique Marc-Linquette, 4th Ouest, 59037 Lille cedex, France
2. Cabinet d’endocrinologie, 62, avenue de Bayonne, 64600 Anglet, France
3. Faculté de médecine et de pharmacie, laboratoire de génétique moléculaire, 22, boulevard Gambetta 76183 Rouen cedex, France

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Correspondence: Jean-Louis Wémeau, CHRU, hôpital Claude-Huriez, 4th Ouest, 59037 Lille cedex, France. jl-wemeau@chru-lille.fr, jean-louis.wemeau@chru-lille.fr

Summary

Polyglandular Autoimmune Syndrome type 1 (PAS-1) or Autoimmune PolyEndocrinopathy Candidiasis-Ectodermal-Dystrophy (APECED) is a rare recessive autosomal disease related to Autoimmune regulator (AIRE) gene mutations. AIRE is mainly implicated in central and peripheral immune tolerance. Diagnosis was classically based on presence of at least two out of three “majors” criteria of Whitaker’s triad (candidiasis, autoimmune hypoparathyroidism and adrenal insufficiency). Presence of one criterion was sufficient when a sibling was previously diagnosed. However, some atypical or poorly symptomatic variants do not correspond to these criteria. As a matter of fact, digestive (malabsorption, pernicious anemia, hepatitis), cutaneous (alopecia, vitiligo, enamel dysplasia) or ophthalmo logical (keratitis) components could prevail. In these cases, diagnosis could be made by molecular genetics. Prognosis is influenced by genetic (AIRE mutations, HLA), hormonal and environmental (infections) factors. Potentially lethal components (hepatitis and severe malabsorption) could be treated by immunosuppressors. Candidiasis and other infections should be carefully screened and treated before beginning those therapies, in order to avoid severe systemic infections.

Polyglandular autoimmune syndrome type 1 (PAS-1) is a rare disease, the diagnosis of which is traditionally based on the identification of at least two out of three components of the triad described by Whitaker [1]: chronic mucocutaneous candidiasis, hypoparathyroidism and adrenocortical failure. If one of the patient’s siblings is affected, only one of the components of the triad is needed to make the diagnosis [2]. The term autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome introduces the concept of ectodermal
dystrophy, which is however not among the required clinical diagnostic criteria. It is a genetic disorder with autosomal recessive inheritance [3], and is attributed to mutations in the autoimmune regulator (AIRE) gene. The first manifestations of the disease generally occur during childhood, although they may appear later. Due to its various clinical expressions, it is of concern to the entire medical community.

PAS-1 can be differentiated from other types of APS. The exceptional IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome), with monogenic transmission, is characterized by the early occurrence of type 1 diabetes, enteropathy, eczema, hypothyroidism and other autoimmune manifestations [4]. It is linked to mutations of the FOXP3 gene, which encodes for the protein scurfin and is essential for the development of CD4+CD25+ regulatory T-cells [4].

The other forms of pyl glandular autoimmune syndromes, which are much more common, mainly affect adult patients. They are polygenic and their occurrence is influenced by the HLA genotype. They were previously distinguished as PAS-2 (which associates adrenocortical failure with autoimmune thyroiditis and/or type 1 diabetes, and sometimes other autoimmune disorders), PAS-3 (combining autoimmune thyroiditis and one or several other autoimmune disorders, with the exception of adrenal involvement), and PAS-4 (combining at least two autoimmune disorders other than those previously mentioned) [2]. However, they are now generally all called PAS-2 or PAS-2/3.

**Epidemiology**

PAS-1 is a rare disease, which is more common in certain populations due to consanguinity or a founder effect, as in Finland [3] where its prevalence has been estimated to be one case per 25,000 [5]. It was one case per 14,400 in Sardinia [6], one case per 9000 in the Iranian Jewish population [7] and one case per 90,000 in the Norweigan population [8]. In a recent study we were able to estimate its frequency in France to be one case per 500,000 among the nine million inhabitants of the northwest regions (Nord-Pas-de Calais, Picardie, Upper and Lower Normandy) [9].

**Pathophysiology**

**Genetic aspects**

The AIRE gene, located on 21q22.3, includes 14 exons [10,11] (figure 1). It is expressed in the thymus (in the epithelial cells of the medulla and the dendritic cells [DC]), the medulla and

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**Figure 1**

**AIRE gene and AIRE 1 protein (according to Meloni [13])**

The AIRE gene is composed of 14 exons; the most widespread mutations are shown in red above the exon carrying it. They are abbreviated as follows: Finnish mutation R257X = c.769C > T (p.Arg257Stop), English mutation 967–979del = c.967–979del13 (p.Leu323SerfsX51), Iranian mutation Y85C = c.254A > G (p.Tyr85Cys), Sardinian mutation R139X = c.415C > T (p.Arg139Stop). The AIRE 1 protein has several functional domains: HSR: Homogeneously Staining Region; homodimerization protein domain; NLS: Nuclear Localization Signal; nuclear localization domain; SAND: DNA liaison domain; PHD: Plant Homedomain) zinc finger: transcription regulation domain; PRR: Proline Rich Region): characteristic region of transcription factors; 4 LXXLL motifs: motifs of nuclear receptor liaison.
paracortical area of the lymph nodes, the spleen, the fetal liver and peripheral blood (monocytes, differenciated DCs and CD4+ T-lymphocytes) [10,12].

The AIRE gene encodes for the 57-kDa AIRE-1 protein, composed of 545 amino-acids (figure 1) [11]. It is primarily localised in the nucleus, but it can be translocated in the cytoplasm [12]. It has typical transcription factor structural characteristics (its various functional domains are shown in (figure 1) [13]). Its role in transcription regulation has been shown in vitro, involving the plant homeo-domains (PHD). It also has transcriptional transactivation properties via the carboxyl terminus of the protein containing a PHD domain and a domain rich in leucine zipper.

More than 50 mutations of the AIRE gene have been described, including deletions, insertions and missense and nonsense point mutations. There are old founder mutations, most of which are widespread in certain populations. The c.769C > T (p.Arg257Stop) mutation is the most common in Finnish patients [10,11], as well as in central and eastern European and northern Italy, evidence of its early introductin in Cauassic populations. In Norwegian, North American, English and Irish populations and in northerwestern France, the c.967-979del13 (p.Leu323SerfsX51) mutation is the most common. The c.254A > G (p.Tyr85Cys) mutation is typical in Iranian Jewish patients, whereas the c.415C > T (p.Arg139Stop) mutation is the most common in Sardinia (figure 1).

Most of these mutations modify the cytoplasmic and nuclear distribution of the AIRE protein. Mutations that affect the HSR domain (Iranian mutation c.254A > G [p.Tyr85Cys]) block the cytoplasmic localisation of AIRE by inhibiting entry of the protein into the nucleus. The Finnish c.769 C > T (p.Arg257Stop) mutation affects the SAND domain, resulting in a truncated protein at its carboxyl terminus; in addition to modification of the protein’s intracellular distribution, its transactivation function is abolished. This mutation thus proves to be very deleterious, resulting in near total loss of the protein function [14].

**Immunological aspects**

**Role of Autoimmune Regulator in the establishment of thymic central tolerance**

The development of a knockout mouse model for the AIRE gene demonstrated its role in central tolerance to self. AIRE -/- mice have spontaneous organ-specific autoimmunity, similar to the human APECED syndrome, though milder. They present a specific reduction or even abolition of ectopic RNA transcript expression (i.e. normally peripherally expressed), usually tissue-specific in the mTEC [15]. Furthermore, in AIRE -/- mice, there is a loss of thymic negative selection of autoreactive T-lymphocytes (essential for the establishment of self tolerance), found in the periphery, which is the source of development of autoimmune disorders [16]. AIRE therefore controls the

**Figure 2**

**Main pathophysiological mechanisms causing central and peripheral tolerance abnormalities**

The role of autoimmune regulator is explained in the upper part of the diagram (a), and the consequences of its absence are in the lower part (b). Lack of central tolerance: AIRE enables the expression of self antigens, which are primarily tissue-specific, by the thymic epithelial cells (mTEC), which leads to deletion of autoreactive T lymphocyte clones. When AIRE is absent, these T-lymphocytes could expand in the periphery, resulting in organ-specific autoimmune diseases. Lack of peripheral tolerance: AIRE also controls the expression of self antigens by the extrathymic Aire-expressing cells (eTAC) in lymph nodes and spleen, which leads to deletion of others autoreactive T lymphocyte clones. When AIRE is absent, these self reactive T-lymphocytes could also expand and be responsible for autoimmun attacks.
expression of ectopic RNA transcripts by the thymic epithelial cells, which is essential for the negative selection of autoreactive T-lymphocytes. For example, it was shown that the loss of AIRE-dependent thymic expression of a peripheral antigen such as mucine 6 in AIRE -/- mice led to the emergence of autoimmunity against this protein [17] (figure 2).

**Role of Autoimmune Regulator in peripheral tolerance**

Moreover, extrathymic Aire-expressing cells (that are present in the spleen and lymph nodes) can also express a diverse array of distinct Aire-dependent self antigens. They interact with autoreactive T-cells and provoke their deletion, and therefore they may help to reinforce immune tolerance by preventing the maturation of autoreactive T-cells that escape thymic negative selection [18] (figure 2).

**Susceptibility to chronic mucocutaneous candidiasis**

Chronic mucocutaneous candidiasis is frequently associated with T-cell immunodeficiencies. Specifically, the proinflammatory IL-17A–producing Th17 subset is implicated in protection against fungi at epithelial surfaces. IL-17F and IL-22 responses to *Candida albicans* antigens are severely reduced in APECED patients affected by candidiasis. These reductions are strongly associated with neutralizing autoantibodies to IL-17F and IL-22, whereas responses were normal and autoantibodies infrequent in APECED patients without candidiasis. Two studies revealed neutralizing autoantibodies to IL-17A, IL-17F and/or IL-22 in APECED patients, especially those with candidiasis. These results suggest that the immunodeficiency underlying candidiasis in APECED has an autoimmune basis. Similar results are found in patients affected by thymomas [19,20].

**Clinical description**

PAS-1 classically associates chronic mucocutaneous candidiasis, autoimmune polyendocrinopathy, non-endocrine autoimmune disorders and ectodermic anomalies. The prevalence of the different disorders varies according to the study (table 1), as does their order of occurrence. The first manifestation of the disease usually occurs in childhood, followed by progressive formation of the other disorders, sometimes in the fifth decade. The three components of Whitaker’s triad generally appear in the first two decades. There is extreme variability amongst patients in the number of clinical manifestations of the disease, ranging from 1 to 10 [21]. This large phenotypic variability may contribute to misdiagnosis, particularly in the atypical forms or those with few symptoms, which do not meet the standard diagnostic criteria.

**Mucocutaneous candidiasis**

This is the most frequent manifestation, with the exception of Iranian Jews in whom it is rarely described. It generally occurs before the age of 5 years, and is often the presenting symptom of the disease [5,7,9,21–23]. In less than 10% of cases, the candidiasis is limited to the skin and is often localized. It mainly affects the oral mucous membranes (up to 100% of patients), the nails (in 2/3 of cases), and more rarely the genitals [5,24]. Oesophageal candidiasis, which causes chest pain and dysphagia, is less common, affecting 15 to 22% of patients [21,24]. Gastrointestinal candidiasis is much rarer and results in chronic diarrhea [21,22]. Rare cases of systemic candidiasis have resulted in death, especially with the use of immunosuppressive treatment [9,21,22]. Nevertheless, the majority of candidiasis cases are moderate but recurrent. They generally respond to long-term oral systemic antifungal agents, although some patients remain resistant to these treatments [24]. Some cases of oral or oesophageal squamous cell carcinoma have been described, occurring as complications of inadequately treated oral candidiasis. Their prognosis is poor [21].

**Autoimmune endocrine manifestations**

Hypoparathyroidism is the most common autoimmune disorder in all studies, with the exception of our French series. It is generally the first endocrine manifestation and usually presents before the age of 10 years [5,7,9,21–23]. It may remain the only endocrine disorder in certain patients, particularly in Iranian Jews and in 20% of Finnish cases [5,7].

Adrenocortical failure is the second autoimmune disorder in order of frequency, occurring before the age of 15 years [5,7,9,21–23]. It usually manifests (in 78% of cases) with both a mineralocorticoid and glucocorticoid deficiency (figure 3a). In 12% of cases however, it may initially present as isolated hypoadosteronism, followed by cortisol deficiency after a variable time period [5,9]. Conversely, cortisol deficiency may initially be isolated in 10% of patients, subsequently followed by mineralocorticoid deficiency after 6 months to 6 years, or even 10 years [5,21].

Primary hypogonadism is found more frequently in women than in men and generally occurs before the age of 30 years, usually during the second decade [5,7,9,21–23]. It can therefore manifest before or just at the start of puberty, resulting in absence of puberty, delayed puberty, primary or secondary amenorrhoea after several cycles in adolescents [21]. Two spontaneous pregnancies occurred in one patient with ovarian insufficiency in our series, evidence of its fluctuating nature [9]. Type 1 diabetes is rare, occurring between the ages of 4 and 37 years [5,7,9,21–23].

Autoimmune thyroiditis, the cause of hypothyroidism, is also rare, generally occurring before the age of 30 years [5,7,9,21–23]. Grave’s disease is not classically described in PAS-1 since only two observed cases have been reported. Autoimmune hypophysitis, also rare, is generally diagnosed between the ages of 5 and 15 years. Among the rare cases described, isolated growth hormone insufficiency is predominant. One case of corticotropin insufficiency and two cases of diabetes insipidus have also been observed [5,7,9,21–23].
Non-endocrine autoimmune manifestations

Autoimmune gastritis occurs in less than 15% of patients with APECED syndrome, at a mean age of 17.2 years [5,7,9,21–23]. In severe forms, chronic atrophic gastritis is complicated by pernicious anemia. One case of gastric adenocarcinoma has been described in APECED syndrome [22].

Malabsorption, which is common in APECED syndrome, occurs at an early age (mean age of 6.6 years) [5,7,9,21–23]. Several aetiologic explanations have been put forth. Autoimmune destruction of the enterochromaffin cells at different levels of the gastrointestinal tract has been suggested, affecting the gastric fundus, duodenal mucosa or the proximal small intestinal mucosa [25,26]. An absence of respective enterochromaffin cells was found on biopsy. For example, in one patient with malabsorption, there was reversible destruction of the enterochromaffin cells of the proximal small intestinal mucosa, resulting in cholecystokinin deficiency and leading to steatorrhea. These cells have significant regenerative potential, which explains the reversible nature of the malabsorption [26]. Moreover, hypocalcemia could be the cause of cholecystokinin deficiency, thus worsening the malabsorption through delayed gallbladder emptying, and pancreatic insufficiency.

Other aetiologies include: intestinal infections (C. Albicans, G. Lambia or C. difficile), autoimmune exocrine pancreatic insufficiency, coeliac disease, intestinal lymphangiectasia and cystic fibrosis of the pancreas [22].

Autoimmune hepatitis occurs with variable frequency and severity at an early age (mean age of 8 years) [5,7,9,21–23]. It can range from an asymptomatic course with spontaneous regression to more severe active chronic hepatitis or even fulminating hepatitis, requiring transplantation or resulting in death [21,22].

Vitiligo, found in less than a quarter of cases, can occur very early, preceding the classical diagnostic components (figure 3a) [5,7,9,21–23]. Its severity ranges from several depigmented spots to diffuse involvement of the entire body surface [21]. Poliosis may be present [24].

### Table 1

<table>
<thead>
<tr>
<th>Clinical manifestations</th>
<th>Finnish series 1990 68 patients (%)</th>
<th>Iranian Jewish series 1992 23 patients (%)</th>
<th>Italian series 1998 41 patients (%)</th>
<th>Norwegian series 2007 36 patients (%)</th>
<th>Personal French series 2010 19 patients (%)</th>
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<tbody>
<tr>
<td><strong>Endocrinopathies</strong></td>
<td></td>
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<td>96</td>
<td>93</td>
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<td>63</td>
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<td>22</td>
<td>73</td>
<td>68</td>
<td>79</td>
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<td>Peripheral hypogonadism</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>F</td>
<td>60</td>
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<td>71</td>
</tr>
<tr>
<td>M</td>
<td>14</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>12</td>
<td>4</td>
<td>2.5</td>
<td>9</td>
<td>5</td>
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<tr>
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<td>3</td>
<td>10</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>ND</td>
<td>ND</td>
<td>7</td>
<td>0</td>
<td>5</td>
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<tr>
<td><strong>Other autoimmune diseases</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Pernicious anemia</td>
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<td>9</td>
<td>15</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>18</td>
<td>ND</td>
<td>15</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>12</td>
<td>ND</td>
<td>20</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Alopecia</td>
<td>29</td>
<td>13</td>
<td>37</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>13</td>
<td>ND</td>
<td>12</td>
<td>20</td>
<td>21</td>
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<td><strong>Mucocutaneous candidiasis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>100</td>
<td>17</td>
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<td><strong>Ectodermic disorders</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Keratopathy</td>
<td>35</td>
<td>ND</td>
<td>12</td>
<td>9</td>
<td>37</td>
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<tr>
<td>Tooth enamel hypoplasia</td>
<td>77</td>
<td>ND</td>
<td>ND</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Nail dystrophy</td>
<td>52</td>
<td>ND</td>
<td>7</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

F: females, M: males, ND: undetermined.
Alopecia is a common component of APECED syndrome and occurs early (mean age of 10.3 years) [5,7,9,21–23]. It may present as hairless patches, sometimes temporary but frequently recurrent, or alopecia of the scalp or even the entire body (figure 3b) [9,21,24].

**Ectodermal dystrophy**

Keratoconjunctivitis is a common symptom, usually occurring before the age of 4 years [5,7,9,21–23]. It is generally bilateral and can lead to blindness if care is not provided early or is inadequate [21]. It is not the consequence of hypoparathyroidism, but often precedes it [22]. In the acute phase patients experience photophobia, blepharospasms and lacrimation; the conjunctiva is red and the cornea is clear, but an isolated or ring-like subepithelial oedema may occur, forming superficial greyish opacities. This first stage is reversible with local corticosteroid therapy. As recurrence is common, the formation of superficial subepithelial scarring and superficial punctated nodules may appear. In the last stage, permanent nodules, panus, corneal leukomas and significant neovascularisation develop.

Tooth enamel hypoplasia, which is not consistently reported, generally starts in the first decade of life and may precede hypoparathyroidism [5,23]. It can affect all teeth, but the canines are usually targeted. The hypoplasia may affect the entire tooth or occur in transverse bands or pits, alternating with normal areas.

Nail dystrophy, occurring inconsistently, is clinically mild and is often overlooked [22,23]. It occurs independent of hypoparathyroidism. An autoimmune mechanism, as with tooth enamel hypoplasia, has been suggested [22].

**Rarer clinical manifestations**

Other disorders, both autoimmune and non-autoimmune, have been described with APECED syndrome [5,7,9,21–23], including: Splenic atrophy: Suspicion is raised by the presence of Howell-Jolly bodies in the blood, thrombocytosis, anisocytosis, or poikilocytosis. A full assessment can be made with liver/spleen scintigraphy or ultrasound. It results in increased susceptibility to infections, particularly pneumococcal, and should be systematically ruled out with abdominal ultrasound.

Severe infectious disorders: bacterial septicemia (*E. cloacae, L. monocytogenes, C. jejuni*), intestinal infections (*C. difficile, G. lamblia*), pulmonary tuberculosis. These infections develop more easily with immunosuppressive therapy.

Mucocutaneous disorders: febrile skin rashes, lichen planus, cutaneous vasculitis, calcification of the tympanic membranes.

Ophthalmologic disorders: cortical lenticular opacities (related to hypoparathyroidism), iridocyclitis, optic atrophy or retinal degeneration.

Clinical forms
Until recently, the diagnosis of APECED syndrome was based on the presence of at least two components of Whitaker’s clinical triad (known as “major criteria”), or on the presence of one of these criterion if one of the patient’s siblings is affected. These diagnostic criteria however lead to misdiagnosis of the atypical forms or those with few symptoms, notably associating a major criterion with certain minor ones (gastrointestinal and skin-hair in particular). Molecular laboratory testing is crucial for the diagnosis of these clinical forms [8,9].

Immunological aspects: the main autoantibodies
Many autoantibodies (AB) have been identified in patients with APECED syndrome. Some are the same as those described in nonsyndromic autoimmune diseases; others have been observed almost exclusively with this disease. However, due to the rarity of the disease, the assay for these specific autoantibodies has not yet been developed in France. Details of the main antigenic targets and their roles are shown in table II.

Tissue-specific autoreactivity
Parathyroid involvement
Parathyroid ABs could be found in APECED syndrome [9,22]. More specifically, ABs against the extracellular part of the calcium-sensing receptor (CaSR), which is present in autoimmune hypoparathyroidism, are sometimes found in the serum of hypoparathyroid patients with APECED syndrome [21]. Their prevalence in this disease however is still lower than in autoimmune hypoparathyroidism, whether isolated or associated with another type of APS. More recently, NALP5-specific autoantibodies were detected in 49% of the patients with APS-1 and hypoparathyroidism but were absent in all patients with APS-1 but without hypoparathyroidism. NALP5 appears to be a tissue-specific autoantigen involved in hypoparathyroidism in patients with APS-1 [26bis].

Adrenocortical involvement
The adrenocortical antibodies (ACA) are very commonly present at the time of diagnosis (93% of cases) but may disappear after several years of disease progression [22]. They are moreover predictive of the occurrence of Addison’s disease. ACA recognize 21-hydroxylase, in addition to 17-hydroxylase and cholesterol side-chain cleavage (SCC) enzymes, which are involved in steroid hormone synthesis. Of these, the presence of anti-21 hydroxylase ABs, which are positive in 75% of patients with Addison’s disease, are the only that are statistically correlated with adrenal failure [27].

Gonad involvement
Steroid cell autoantibodies (SCA) specifically target the cytoplasmic antigens of steroid-producing cells present in the adrenal glands, gonads and placenta. They are considered serologic markers of peripheral hypogonadism, and the target antigens of this autoreactivity are 17-hydroxylase and SCC [22]. Only the SCC antibodies are markers of hypogonadism in women with APECED syndrome [27]. They may be present in men but do not appear to be associated with testicular involvement [8].

Pancreatic islet cell involvement
Glutamic acid decarboxylase 65 (GAD65) antibodies are present in 40% of patients with APECED syndrome, but they have a poor specificity and a low positive predictive value, just as the islet cell autoantibodies (ICA) in PAS-1. They are however the most sensitive antibodies in PAS-1 (72% for GAD65 ABs and 54% for the ICA) [27]. In contrast, insulin autoantibodies and IA2 (tyrosine phosphatase) autoantibodies are much more specific (100% and 96%, respectively), with a good positive predictive value of 67% in APECED syndrome. Their sensitivity is low (33%). Only the IA2 autoantibodies are significantly associated with type 1 diabetes [27].

Thyroid involvement
Thyroid peroxidase (TPO) autoantibodies were present in all patients with thyroiditis in two series, while thyroglobulin (Tg) autoantibodies were only found in one out of two cases of thyroiditis [22,28]. TPO ABs were present in 27% of patients with no clinical evidence of thyroapathy and with no development of it at the last follow-up [22]. Likewise, Tg ABs were found in 28% of patients with no thyroid disease [28]. Their presence therefore is not very specific, and their prognostic value is low in this disease.

Pulmonary involvement
Autoantibodies to KCNRG (a putative potassium channel regulator), a protein mainly expressed in bronchial epithelium, are strongly associated with pulmonary involvement such as bronchiolitis obliterans in PAS-1 [29].
### Table II

**Main known antigenic targets in patients with Polyendocrinopathy Candidiasis-Ectodermal-Dystrophy syndrome**

<table>
<thead>
<tr>
<th>Disease component</th>
<th>Tissue affected</th>
<th>Antigenic target</th>
<th>Role of the antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocortical failure</td>
<td>Adrenocortical</td>
<td>21-hydroxylase&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Biosynthesis of steroid hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17α-hydroxylase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side-chain cleavage enzyme (SCC)</td>
<td></td>
</tr>
<tr>
<td>Hypoparathyroidism</td>
<td>Parathyroid</td>
<td>NALP5</td>
<td>Calcium homeostasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcium-sensing receptor</td>
<td></td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Ovarian and testicular</td>
<td>17α hydroxylase</td>
<td>Biosynthesis of steroid hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side-chain cleavage enzyme (SCC)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Endocrine pancreas</td>
<td>Glutamic Acid Decarboxylase (GAD65)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>GABA biosynthesis</td>
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<td></td>
<td></td>
<td>Insulin</td>
<td>Glucose homeostasis</td>
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<tr>
<td></td>
<td></td>
<td>Tyrosine phosphatase (IA2)&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Thyroid</td>
<td>Thyroid peroxidase&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Biosynthesis of thyroid hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroglobulin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Thyroid hormone precursor</td>
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<tr>
<td>Pulmonary disease</td>
<td>Lung</td>
<td>KCNRG&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Putative potassium channel regulator</td>
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<tr>
<td>Atrophic gastritis/Pernicious</td>
<td>Gastric mucosa</td>
<td>Intrinsic factor&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Malabsorption</td>
<td>Gastrointestinal tract</td>
<td>Glutamic Acid Decarboxylase (GAD65)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>GABA biosynthesis</td>
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<td></td>
<td></td>
<td>Histidine decarboxylase&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Histamine biosynthesis</td>
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<td></td>
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<td>Tryptophane hydroxylase&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Steroid biosynthesis (1st step)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Liver</td>
<td>AADC&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Biosynthesis of dopamine (2nd step)</td>
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<tr>
<td></td>
<td></td>
<td>Cytochrome P450 1A2&lt;sup&gt;1&lt;/sup&gt;</td>
<td>and serotonin (2nd step)</td>
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<tr>
<td></td>
<td></td>
<td>Cytochrome P450 2A6</td>
<td>Transport of electrons and hydroxylation</td>
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<td>Cytochrome P450 1A1</td>
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<td></td>
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<td>Cytochrome P450 2B6</td>
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<tr>
<td>Vitiligo</td>
<td>Skin</td>
<td>SOX 9</td>
<td>Transcription factors</td>
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<td>SOX 10&lt;sup&gt;1&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>AADC&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Alopecia</td>
<td>Hair follicle</td>
<td>Tyrosine hydroxylase&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Biosynthesis of catecholamines and indolamines</td>
</tr>
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</table>

AADC: aromatic l-amino acid decarboxylase.

<sup>1</sup>Best marker of the corresponding clinical manifestation.

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**Gastric involvement**

Markers of autoimmune gastritis in APECED syndrome are the same as those found in the general population. These are gastric parietal cell (GPC) antibodies in indirect immunofluorescence (IFI) and intrinsic factor (IF) antibodies, which would also have a good predictive value in this disease [22,28].

**Malabsorption**

In cases of autoimmune destruction of the enterochromaffin cells of the gastrointestinal tract, the autoantigens specifically identified in PAS-1 are enzymes involved in neurotransmitter synthesis. For example, autoreactivity against an enzyme involved in the synthesis of serotonin, known as tryptophane hydroxylase (TPH), is seen in 45 to 50% of patients with APECED syndrome [27,30], and the presence of TPH autoantibodies is significantly associated with the occurrence of malabsorption [27,30]. Likewise, autoreactivity against histidine decarboxylase (HDC), the enzyme involved in histamine synthesis, is found in 37% of patients with APECED syndrome. It is associated with the occurrence of intestinal dysfunction with autoimmune...
Polyglandular Autoimmune Syndrome Type I

destruction of the enterochromaffin cells (which produce histamine in the gastric fundus) [31]. Finally, the presence of GAD 65 ABs (enzyme expressed in the intestinal nerve plexus) is also statistically linked to malabsorption in APECED syndrome [27] but not to the occurrence of type 1 diabetes.

**Hepatic involvement**

Liver kidney microsomal type 1 antibodies (LKM-1) are seen in 50 to 75% of APECED patients with autoimmune hepatitis, but their antigenic target is different from that observed in the general population, cytochrome P450 2D6 [28,32]. The autoantigens detected were primarily identified as cytochromes P450 2A6, P450 1A2, P450 1A1 and P450 2B6 [32]. Among them, only the cytochrome P450 1A2 antibodies are markers of hepatic involvement, with a high specificity (100%) but low sensitivity (50%) [27,32]. Antibodies against aromatic L-Amino acid decarboxylase (AADC, enzyme for the biosynthesis of catecholamines and indoleamines) are also hepatic antigenic targets in APECED syndrome. In a study of 90 patients with APECED, antibodies against cytochrome P450 1A2, AADC and TPH (also described as markers of intestinal involvement) were significantly associated with hepatic involvement [27]. AADC and CYP1A2 are expressed in the liver (unlike TPH), suggesting that ABs directed against these enzymes could play a pathogenic role [27].

It should be noted that antismooth muscle antibodies, which are standard markers of autoimmune hepatitis in the general population, do not have this distinction in APECED syndrome [32].

**Cutaneous involvement**

In APECED patients with vitiligo, antimelanocyte ABs have been detected, though they may also be present in unaffected patients [22]. More recently, autoreactivity against two transcription factors, SOX9 and SOX10, was shown in 15 and 22%, respectively, of patients with APECED syndrome. SOX10 is a transcription factor involved in the differentiation of the neural crest and is expressed in the melanoblasts of mice; it shares epitopes with SOX9. In APECED syndrome, 63% of patients with vitiligo have SOX10 ABs [33]. In addition, the AADC ABs are significantly associated with the presence of vitiligo, although their role in its occurrence is still uncertain [27].

In APECED patients with alopecia, ABs directed against the cytoplasm of hair follicle keratinocytes have been described. They are present in 13% of patients and are significantly associated with the presence of complete scalp baldness. In addition, an enzyme involved in dopamine synthesis, tyrosine hydroxylase (TH), is antigenic in 44% of patients with PAS-1. The presence of anti-TH ABs is significantly associated with alopecia in these patients [34].

**Non-tissue-specific autoreactivity**

Antinuclear antibodies (ANA) have been detected at low titers in APECED syndrome, with a prevalence close to that of the general population [28,32]. IgG autoantibodies against interferon (IFN) have been identified in the serum of patients with APECED syndrome [8,35]. They have a neutralising activity and are primarily directed against IFN-α, but also against INF-γ. In this study, both types of ABs were present in all the patients, demonstrating excellent sensitivity (100%). Their titers are very high, particularly in young subjects, and they may appear before the first autoimmune clinical manifestations, or even candidiasis. Although absent in healthy controls and heterozygotes, they may be found in patients with thymoma, though at lower levels. Their exact role has yet to be determined [35]. Presence of circulating antiinterferon autoantibodies at a very early stage is described in PAS-1, and their presence could be considered as an early diagnostic marker of the disease.

**Prognosis**

Due to the wide phenotypic variability of APECED syndrome, research has been done to identify prognostic factors. An association has been reported between early first manifestations of the disease and a greater number of disease effects. Likewise, patients who present the first clinical manifestations later are more likely to develop fewer components of the disease [2,25,22]. Research for a genotype-phenotype correlation showed that candidiasis occurred more frequently in the presence of an allele with the predominant Finnish mutation, c.769C > T (p.Arg257Stop) [36]. We found a correlation between the presence of alopecia and that of the most widespread mutation in English-speaking populations, c.967-979del13 (p.Leu323SerfsX51) [9]. However, due to the presence of very different phenotypes for the same genotype, including even among siblings, other factors have been investigated. For example, the HLA system has an influence on the occurrence of type 1 diabetes, Addison’s disease and alopecia. The predisposing or protector HLA haplotypes with regard to these different effects are identical to those found in the general population [36]. In addition, male sex has a protective effect from parathyroid involvement [21], and women seem to be more susceptible to alopecia [24] and gonad effects [5,21,22]. Environmental factors, particularly the immunogenic role of infectious agents, have also been suggested. Patients with PAS-1 generally die early, with those in the last large Finnish series dying at a mean age of 34 years, even though overall survival has improved in the last 2 decades [21]. The main causes of death directly related to APECED syndrome are, in order of frequency: squamous cell carcinoma of the mouth or oesophagus, fulminating hepatitis, severe infections and septicemia, diabetic ketoacidosis, complications of
hypoparathyroidism, acute adrenal failure, and renal failure and its complications [5,21,22]. Several patients with psychological or social adjustment disorders were found isolated in their homes, dead or dying [21].

**Treatments**

**Hormone replacement therapy**

The primary manifestations of APECED syndrome have traditionally been treated symptomatically. Endocrine involvement is treated with hormone replacement. Parathyroid hormone deficiency presents several distinctive features in this regard. Attempts to compensate for the deficiency may be difficult due to significant variability in the serum calcium levels of these patients, and the associated risks of hypercalcemia related to vitamin D treatment, hypomagnesemia or malabsorption. It is often unrealistic to normalise serum calcium levels, and the therapeutic objective is then to avoid the clinical signs of hypocalcemia while maintaining values between 2 to 2.2 mmol/l. Urine calcium levels should remain below 0.1 mmol/kg in order to avoid the harmful effects of hypercalcemia (nephrocalcinosis, renal failure). Hypomagnesemia, often present with malabsorption, should be corrected. In cases of malabsorption (which itself is worsened by hypocalcemia), an increase in the dosage of the vitamin/calcium treatment, a decrease in fat intake or replacement with medium-chain triglycerides can improve serum calcium levels [37]. In the treatment of adrenocortical failure, any overdose of glucocorticoids, which is potentially harmful to the bones, should be avoided in subjects with hypogonadism. Increased sensitivity to mineralocorticoids has been reported, resulting in a risk of hypertension and hypokaliemia, which may be difficult to control.

**Anti-infective therapy**

Candidiasis infections require standard antifungal agents. Amphotericin B can be used as first-line treatment, though the infections may be resistant. Treatment with ketoconazole, fluconazole or itraconazole are then effective [22,24,37]. Terbinafine has also been tried. Consecutive courses of itraconazole have been successfully used to treat resistant strains [24]. Localized forms of candidiasis, particularly oral, should be eradicated, since squamous cell carcinomas of the mouth have mainly been described following inadequate local antifungal treatments (courses too short, insufficient dose, failure to switch to systemic therapy). Furthermore, systematic investigations for underlying candidiasis and its treatment before starting immunosuppressive therapy appear necessary in order to avoid the occurrence of potentially fatal systemic candidiasis [9].

Finally, an annual pneumococcal vaccination is recommended in cases of splenic atrophy. In non-responder patients, and particularly in the presence of splenic parenchyma on abdominal ultrasound, consecutive courses of prophylactic antibodies may be proposed [37].

**Immunosuppressive treatments**

Hepatic involvement and severe malabsorption in APECED syndrome require an aggressive therapeutic approach since they are life-threatening. For example, ciclosporin or azathioprine for autoimmune hepatitis, and methotrexate for severe malabsorption, either with or without corticosteroid therapy, have been used with good results [9,21,38–40]. We regretfully experienced the death of a patient with large granular lymphocytic leukemia with erythroblastopenia treated with cyclophosphamide, due to septicemia from *C. Albicans* and *S. Aureus* [9].

Immunosuppressive agents have also been used exceptionally for kidney or liver transplantation [21,41]. Follow-up in these studies was short, and although the disease for which the immunosuppressant was started generally improved, the results for associated autoimmune diseases remain inconsistent. The associated autoimmune symptoms thus improved in certain cases [9,41], although this did not prevent the occurrence of new autoimmune manifestations in others [9,40]. In our study, four patients were treated with immunosuppressive therapies, in three specific indications: autoimmune hepatitis, severe malabsorption with statural retardation and undernutrition in a child and LGLL. These therapies were effective for the disease component they were supposed to treat, and patients developed no new autoimmune components under these treatments, which has not always been the case in other reports [42]. Anti-CD20 therapies such as Rituximab have been successfully tested in Aire KO mice and more recently in an PAS-1 patient, to treat pulmonary disease [43,44].

Testing for splenic atrophy (which promotes the occurrence of infections) in these conditions is also vital, since its presence justifies close monitoring; vaccinations and prophylactic anti-pneumococcal antibiotic therapy are especially recommended under these conditions.

**Conclusion**

APECED syndrome, or Polyglandular autoimmune syndrome type 1, remains a exceptional disease, both in terms of frequency and its pathophysiological mechanisms. Due to the great diversity of its clinical expression, it is of concern to the entire medical community and should not be overlooked due to its potential seriousness. Particular attention should be given to the diagnostic work-up of atypical forms and those with few symptoms, with the formal diagnosis based on molecular genetics. The visceral forms are life-threatening and require aggressive immunosuppressive therapy.

**Disclosure of interest:** the authors declare that they have no conflicts of interest concerning this article.
Polyglandular Autoimmune Syndrome Type I

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