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Review

Thyroid autoimmunity and polyglandular endocrine syndromes

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ABSTRACT

Even though autoimmune thyroiditis is considered as the most emblematic type of organ-specific autoimmune disorder of autoimmunity, autoimmune thyroid diseases can be associated with other autoimmune endocrine failures or non-endocrine diseases (namely vitiligo, pernicious anemia, myasthenia gravis, autoimmune gastritis, celiac disease, hepatitis). Thyroid disorders, which are the most frequent expression of adult polyendocrine syndrome type 2, occur concomitantly with or secondarily to insulinodependent diabetes, premature ovarian failure, Addison's disease (Schmidt syndrome, or Carpenter syndrome if associated with diabetes). Testicular failure and hypoparathyroidism are unusual. The disease is polygenic and multifactorial. Disorders of thyroid autoimmunity are, surprisingly, very rare in polyendocrine syndrome type 1 (or APECED) beginning during childhood. They are related to mutations of the *AIRE* gene that encodes for a transcriptional factor implicated in central and peripheral immune tolerance. Hypothyroidism can also be observed in the very rare IPEX and POEMS syndromes.

Key Words: APECED, IPEX, POEMS, polyendocrine syndrome, thyroid, thyroid autoimmunity

Autoimmune thyroiditis is commonly cited as the paradigm of the organ-specific autoimmune diseases. However, Graves' ophthalmopathy, pretibial myxedema, acropachy, some glomerulopathies related to immune complexes binding thyroglobulin and possibly also the controversial entity of Hashimoto's encephalopathy present overt evidence that autoimmune thyroidopathies have extra-thyroidal expressions.[1]

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Moreover, autoimmune thyroiditis can be associated with other endocrine disorders. Even before the 1912 description of Hashimoto's thyroiditis, thyroid disorders appear to have been a common feature of the multiple polyglandular failure described in 1904 by Paul Ehrlich in Germany and in 1908 by Claude and Gougerot in France. Later, Schmidt underlined the specific coincidence of idiopathic adrenal failure with current thyroiditis, while Carpenter noticed the frequent occurrence of diabetes in patients with the Schmidt syndrome.[2] In 1980, Neufeld and colleagues proposed, in a pediatrics review, four types of autoimmune polyglandular syndromes: type 1 Addison's disease, hypoparathyoidism, chronic muco-cutaneous candidiasis, type 2 adrenal failure + autoimmune

thyroid disease, type 3 autoimmune thyroid disease + other auto-immune disease except adrenal failure, type 4 association of other autoimmune endocrine disorders.[3] However, individualization of types 2, 3 and 4 are not really justified by epidemiological, genetic or pathogenic features.[4] Therefore, polyendocrine autoimmune syndromes (PEAS) are now more commonly divided into two types: the rare juvenile PEAS 1 and the more frequent adult PEAS 2[4] (Table 1). Polyendocrine is somewhat of a misnomer since many of the manifestations of the diseases do not concern endocrine organs.

Here we will focus on thyroid diseases observed in patients suffering from the two types of PEA. We will also consider thyroid disorders observed in the very rare IPEX (Immunodysregulation Polyendocrinopathy Enteropathy X-linked) and POEMS (Polyneuropathy, Osteomalacia, Endocrinopathies, Monoclonal dysglobulinemia, Skin disorders) syndromes.

POLYENDOCRINE SYNDROME TYPE 1 (OR APECED: AUTOIMMUNE POLYENDOCRIOPATHIES, CANDIDIASIS, ECTODERMAL DYSTROPHY)

The disease is rare with an incidence lower than 1 in 100,000 inhabitants per year.[4,5] A higher prevalence is observed in some populations, regarding a founder effect or consanguinity: 1 case per 25,000 in Finland, 1 per 600 to 9,000 in Iranian Jews and in Sardinia. In a population of 9 million inhabitants in North-Western France, we observed 19 cases, suggesting a prevalence in France of 1/500,000.[6]

The disease is genetically determined by an autosomal recessive transmission. Parents are safe, but the disease is statistically clinically evident in 1 child out of 4.

The disease was first reported in 1929 by Thorpe and Hardley in a 4-year old child suffering from tetanus and mycelial stomatitis. In 1956, Whitaker described the emblematic triad: adrenal insufficiency, hypoparathyroidism and moniliasis.[7] A more complete description of the disease and mention of ectodermic dystrophia were furnished in Finland by Ahonen,[8] while the relation to mutations on the 21st chromosome was reported in 1994.[9] Eventually, the disease was related to abnormalities of the *AIRE* gene, on the long arm of 21st chromosome comprised of 14 exons.

The *AIRE* gene encodes for the AIRE protein. The AIRE protein is a transcriptional factor expressed in the thymus (medullary thymic epithelial cells, dendritic cells), spleen, lymph nodes (stromal cells), monocytes and CD4 lymphocytes. AIRE interferes with immune regulation. At the thymus level, the AIRE protein contributes to the negative selection of autoreactive thymocytes. Therefore, its impairment allows the production and spread of autoreactive lymphocytes active against proteins of the *one self*. At the peripheral level, the AIRE protein is expressed in eTACs (extra-thymic Aire expressing cells) and controls the proliferation of autoreactive lymphocytes. Finally, AIRE also regulates reactions against microbial agents, especially against mycosis. The T helpers have a natural immune activity against Candida Albicans. AIRE deficiency leads to alteration of intracellular communication between monocytes and T helpers. Moreover, emergence of antibodies against interleukin 17 and 22 was recently demon-

Table 1. Thyroid diseases in the polyendocrine syndromes

Denomination	PEAS 1 APS 1 APECED Juvenile Autoimmune Polyendocrinopathy	PEAS 2 APS2
Frequency	Rare	Common
Occurrence	Childhood onset	Adult onset
Transmission	Monogenic (AIRE)	Polygenic (HLA)
Main features	Hypoparathyroidism Addison's disease Candidiasis RARE THYROID DISEASES	Diabetes Addison's disease Ovarian failure FREQUENT THYROID DISEASES

strated; interleukin 17 and 22 also develop protection against fungal infections.[10,11]

The main feature of APECED syndrome is Whitaker's triad. Candidiasis, which is very frequent and precocious, affecting the mouth and intestinal tractus, appears to be moderately sensitive to antimycosis drugs. Bacterial infections, for example otitis, are also common. Hypoparathyroidism often reveals the disease, determines tetanus and can be corrected by a conventional dose of active forms of vitamin D + calcium. Parents and patients need to be informed about the risk of adrenal insufficiency, which is sometimes dramatically brought to light by an acute crisis.

Diabetes mellitus is uncommon, affecting less than 1 patient in 5. Hypogonadism is predominant in females. Vitiligo and alopecia are frequently encountered: they may be localized or more diffuse and are sometimes universal. Malabsorption can be explained by: candidiasis, celiac disease, intestinal lymphangiectasies, and failure of cholecystokinin production, pancreatic insufficiency and/or hypocalcaemia and auto-immune attack of entero-chromaffin cells.[6]

Another expression of the disease is progressive splenic atrophy, sometimes suspected via the presence of Howell-Jollies bodies; it must be systematically investigated since it contributes to infections and requires pneumoconal vaccination. Hypersensitivity to glycyrrhizin can explain the occurrence of high blood pressure with hypokalemia. Recently, a high frequency of bronchiolitis was described in Sweden and in France.[12] Hemolytic anemia, large granular lymphocyte leukemia, pulmonary hypertension and ocular and neurological impairment in the Vogt-Koyanagi-Harada syndrome can also be observed.[6,13]

Table 2 summarizes the prevalen ce of diverse manifestations of APECED. Hypoparathyroidism is present in 2/3 of patients, Addison's disease and candidiasis in about 80%, apart from the Iranian Jews, who present alopecia in 50% in the our French series.[6]

The lack of specificity of autoantibodies needs to be underlined. GAD65 is a weak predictor of diabetes and is more commonly observed in patients who will develop malabsorption by immunization against enterochromaffin cells. Another striking point is that in PEA1 antigenic sites are uncommon. New techniques have been developed for the detection of antibodies: for example, antiinterferon antibodies with a sensitivity near 100%, antibronchiolar antibodies directed against KCNRG antigen, antipituitary antibodies

Table 2. Clinical features in the polyendocrine syndromes type 2[6]

	Finnish series 1990 68 patients	**Iran Jude series 1992 23 patients**	**Italian series 1998 41 patients**	**Norwegian series 2001 20 patients**	**Our French series 19 patients**
ENDOCRINOPATHIES					
Hypoparathyroidism	79%	96%	93%	85%	63%
Adrenal insufficiency	72%	22%	73%	80%	79%
Hypogonadism	60% F	3 F	60% F	51% F	71% F
	14% H	3 H	0 H	0 H	0 H
Type 1 diabetes	12%	4%	2,5%	0	5%
Hypothyroidism	3%	3%	10%	10%	5%
Hypophysitis	ND	ND	7%	0	5%
OTHER AUTOIMMUNE DISORDERS					
Pernicious anemia					
Malabsorption	13%	9%	15%	0	21%
Hepatitis	18%	ND	15%	10%	26%
Alopecia	12%	ND	20%	5%	11%
Vitiligo	29%	13%	37%	40%	53%
	13%	ND	12%	25%	21%
MUCO-CUTANEOUS CANDIDIASIS	100%	17%	83%	85%	89%

against TDRD6 or ECE2 and antiparathyroid antibodies against anti NALP5, while antibodies against anti-calcium sensor are rare in APECED.

The specific type of mutations may influence the phenotype, even though great phenotypic variability for one and the same genotype is observed. HLA antigens class II DR3/DR4 predispose to type 1 diabetes and autoimmune thyroid diseases. Male gender is protective against hypoparathyroidism, while females develop more alopecia and gonadal insufficiency. The immunogenic rule of infections has also been demonstrated.

Autoimmune thyroid diseases are rarely expressed in PEA1: there was one patient with hypothyroidism at 8 years and four with antiTPO in our series (19 cases), the incidence normally being 0-13% in the literature, but 25% in Slovenia.[14] The median age of occurrence of thyroid disorders has been cited as 20 years according to Betterle,[15] 26.5 years according to Perheentupa.[16] The most frequent expression was Hashimoto's thyroiditis or atrophic thyroiditis. Graves' disease is very rare with only two cases having been reported.[13,17]

One particular form of the disease was described in an Italian family with APECED closely cosegregrating with hypothyroid autoimmune thyroiditis. Surprisingly, inheritance was autosomal dominant and not recessive, as is usually noted. In this family a mutation directed against gene *G228W* was observed.[18] It was subsequently demonstrated that the mutation *G228W* affects the SAND domain of the AIRE protein, modifies its cellular localization and has a dominant negative effect by binding to the wild non-mutated AIRE protein, this pointing to a mechanism which commonly also explains the resistance to thyroid hormones.

POLYENDOCRINE SYNDROME TYPE 2

PEA2 is clearly better known and commoner than APECED. Prevalence is about 4-5 per 100,000 inhabitants. Females are three times more frequently affected than males. Occurrence is commonly observed in adults at ages 20-60 years, mostly in the third or fourth decade, although incidence in childhood is also observed.[4]

Inheritance of PEA2 is also more complex: it appears to be autosomal dominant with incomplete penetrance,[19] as attested by lack of concordance in monozygotic twins. This suggests the contribution of environmental factors, such as bacterial and viral infections, medications, psychological factors, etc. Cases of PEA2 were found to arise after therapy for hepatitis or leukemia with interferon alpha.[20,21] Emergence of PEA2 is also influenced by steroids, sexual hormones and pregnancies.

An imbalance between effector and regulatory T lymphocytes is the major determinant of the autoimmune polyendocrine diseases. A subgroup of T cells recognizes peptides of target organs. HLA alleles determine specific tissue targeting. B lymphocytes stimulated by T lymphocytes produce autoantibodies. T lymphocytes also contribute to cellular damage.[22]

The Major Histocompatibility System has the highest implication, being dependent on polymorphisms of the human leucocyte antigen (*HLA*) gene on chromosome 6. Some frequent associations with HLA haplotypes and manifestations observed in PEA2 are summarized in Table 3.

There is also a contribution of a cytotoxic T lymphocyte-associated (*CTL4*) gene located on chromosome 2q33 to the genetic susceptibility to thyroid antibody production.[23,24] *CTLA-4* modifies T cell activation and interacts with antigen presenting cells.[25] Moreover, there is high additional relation of PEA2 to MIC-A (MHC class 1 chain-related A), a non-classic HLA molecule.[26] Finally, the protein tyrosine phosphatase non-receptor 22 *(PTPN22)* encodes an

Table 3. Associations between HLA haplotypes and manifestations of PEA2 (according to 4, 41)

Haplotype HLA A1, B8, DR3, DQA1*0501, DQB1*0201 = multiple autoimmune component diseases of PEA2
Haplotype HLA DR4-DQB1*0302 = beta-cell autoimmunity only
Haplotypes HLA DR3/4, DQ2/DQ8, DRB1*0404 = risk of Addison's disease
Haplotype HLA DR5 = Schmidt syndrome, HLA DRB1*13 = vitiligo
HLA DQB1*03, DRB*1104, DRB1*0401, and DQB1*0301: alopecia
HLA DR2: protective

intracellular lymphoid tyrosine phosphatase (LPY) with negative regulatory effects on T-cell activation.[27]

In a cohort of 60 Tunisian patients with high incidence of autoimmune thyroid disease and type 1 diabetes, some non-HLA autoimmunity genetic factors were demonstrated as contributors to autoimmune polyglandular syndrome type 2.[28] In Japanese patients with thyroid autoimmune disease (AITD) and type 1 diabetes (TD1) defined as autoimmune polyglandular syndrome type 3, a female predominance, a slow and older age onset of T1D and a higher prevalence of anti-GAD were observed, compared to T1D without AITD. Differences between the two groups may reflect distinct genetic backgrounds including the HLA DRB1-DQB1 haplotypes and *CTL4* gene polymorphisms.[29]

Table 4 summarizes prevalence of the main features of the PEA2: autoimmune thyroid diseases, diabetes, Addison, gonadal insufficiency with premature ovarian insufficiency, vitiligo, alopecia and pernicious anemia. Testicular failure is rare.

In the recent series of 125 cases summarized by G Kahaly,[4] the most frequent combinations were type 1 diabetes and AITD in 41%, AITD and Addison's disease (the Schmidt syndrome) in 15%, followed by diabetes + vitiligo or AITD + vitiligo in 10%.

A long period between cellular loss and overt autoimmune disease is observed. At this time, circulating antibodies can be detected, aiding in assessment of the risk of the endocrine emergency. The shortest interval is between Addison and AITD, the longest between diabetes or vitiligo and thyroid diseases. It is noteworthy that almost 70% of the patients with Addison have a concomitant autoimmune thyroiditis.

Table 4. Prevalence of clinical diseases in the polyendocrine syndromes type 2 in a series of 360 patients.[42]

Sex ratio F/H	3/1
AITD	66%
Diabetes %	61%
Addison %	19%
Gonadal insufficiency %	5.3%
Vitiligo %	20%
Alopecia %	6%
Pernicious anemia %	5.3%

In daily practice, some high-risk associations have to be underlined: e.g diabetes and Addison, type 1 diabetes and hypopituitarism, since patients have a higher risk of hypoglycemia.

Hypothyroidism can determine disorders of growth disorders, but this raises the question of growth hormone (GH) deficiency. Treatment with GH of patients suffering from hypopituitarism leads to disclosure of some central hypothyroidism, or else modifies the need for substitutive doses of levothyroxine.[30,31] Hypothyroidism reduces the need for insulin and can be responsible for hypoglycemia. Since thyroxine replacement enhances cortisol clearance, correction of hypothyroidism can precipitate adrenal crisis in patients with subclinical adrenocortical failure. Finally, high TSH levels are common in patients in whom adrenal insufficiency is discovered and may sometimes be corrected with hydrocortisone supplementation.[32-34]

Graves' disease induces determines glucose intolerance and coincides with diabetes in 3% of cases. Hyperthyroidism can also be revealed by an acute disequilibrium of Addison's disease.[4]

An unrecognized endocrine disorder, mainly autoimmune thyroiditis, is observed in about 1 in 7 first degree relatives of patients with PEA2,[35] thus routine screening of TSH measurement should be seriously considered in this population. However, genetic typing is neither really efficient nor recommended, since PEA2 is polygenic and multifactorial.

IPEX SYNDROME (IMMUNODYSREGULATION POLYENDOCRINOPATHY ENTEROPATHY X-LINKED SYNDROME)

The IPEX syndrome is even rarer than the APECED syndrome. It appears in very early childhood in males. The disorder manifests with psoriasiform or eczematous dermatitis, nail dystrophy, autoimmune skin conditions such as alopecia universalis, bullous pemphigoid, food allergy, infections and severe enlargement of the secondary lymphoid organs and, lastly, autoimmune endocrinopathies: insulindependent diabetes, hypothyroidism.[36] Transmission is monogenic, related to the *FOXP3* gene which codes for the scurfin protein.[37] Scurfin is a transcriptional activator factor which has a key role

for the regulatory T cells. There has been limited success in treating the syndrome by sirolimus or bone marrow transplantation.[38]

POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

POEMS are observed in adults of both sexes. It is characterized by the following associations: severe Peripheral neuropathy, Organomegaly (splenomegaly, hepatomegaly, adenopathies), Endocrinopathies (mainly hypothyroidism, diabetes, gonadal insufficiency), Monoclonal gammopathy, and finally Skin disorders (hyperpigmentation, hypertrichosis, skin thickening). There is as yet imperfect understanding of the nosology and pathogenesis of these types of associations and therefore no medical approach has been established.[39]

In a series of 24 cases of POEMS, 11 cases of clinical and 6 cases of subclinical hypothyroidism have been observed.[40] Hypothyroidism as a cause of edema/effusions in POEMS has been suggested.[40]

CONCLUSION

Thyroid disorders are very rare, in fact virtually anecdotal, in patients with PEA type 1, IPEX and POEMS. It appears puzzling that such severe disorders of general autoimmunity should attack the thyroid gland, the most closely proximal to the thymus.

On the other hand, thyroid autoimmunity is the most frequent disorder observed in patients with PEA type 2, its expressions being very common: thyroid atrophy, hypertrophic goiter related to Hashimoto's thyroiditis, Graves' disease, asymptomatic autoimmune thyroiditis, etc. It should be noted here that a rigorous assessment of the severity of the autoimmune thyroid disorders by the detection of Thyroid Peroxidase Antibodies (TPOAb) may be not so essential in treating the thyroid disorders per se since their prognosis is more or less benign. However, the degree of the ensuing hyper- or hypothyroidism may adversely affect the course of the associated endocrine disorders. Thus, an assessment of the severity of the autoimmune thyroid disorders may help in evaluating the therapeutic options towards the associated endocrine disorders.

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