The General Practice Guide to Autoimmune Diseases

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Autoimmune polyendocrine syndromes

Helena Silva, Joana Rema, Marilda Santos, João Pedro Ramos, Carlos Dias

1 Introduction

Polyendocrine autoimmune syndromes, as a concept, include a large variety of diseases, ranging from non-organ specific auto-immunity (such as systemic lupus erythematosus, SLE) associated with antibodies addressed to insulin receptors or others, through to organ tumours associated with subsequent endocrinopathy, Graves' disease associated with anti-insulin syndrome, and a significant number of other non-endocrine pathologies with effects in the endocrine environment.

Nonetheless, the designation of autoimmune polyendocrine syndromes (APS) (or polyglandular autoimmune syndromes or PGA) is usually reserved to very rare genetically mediated diseases with a constellation of multiple endocrine gland failures, secondary to immune mediated mechanisms of glandular cell destruction resulting in gland dysfunction or atrophy. APS result from a breakdown in tolerance to several organ-specific antigens that can be either monogenic or a result of a complex genetic background, with an eventual environmental trigger. Four main syndromes have been described based on clinical findings alone and designated as APS-1, 2, 3 and 4. APS-1, or Whitaker syndrome, is a very rare disease that usually appears before 20 years of age and is characterized by the association of at least two of the following: chronic candidiasis, chronic primary hypoparathyroidism and/or Addison's disease. Hence the reason it is also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy or APECED. APS-2, or Schmidt syndrome, affects mostly adult women and represents the combination of Addison's disease with autoimmune thyroid disease and/or type 1 Diabetes mellitus. APS-3 is the most common of all four and includes those patients that present autoimmune thyroid disease associated with autoimmune diseases other than Addison's disease or hypoparathyroidism. Other combinations of autoimmune diseases not included in the previous groups are classified as APS-4.

2 Clinical manifestations

The main clinical presentation of APS-1 includes:

1. Chronic candidiasis (CC), usually occurring as the first manifestation and in the first months of life; it may affect nails, skin, tongue, mucous membranes and, less frequently, the oesophagus with oesophagitis and oesophageal strictures.
2. Chronic hypoparathyroidism (CH) frequently preceding Addison's disease (AD) and most commonly before the age of 15; the most frequent features of CH are those related to chronic hypocalcaemia as described in Table 1. The most apparent sign is tetany, which may vary from a latent form (demonstrated by Chvostek's and Trousseau's signs or electromyography), to painful muscle spasms (usually starting distally in the limbs with centripetal progression, from carpopedal spasms and facial grimacing, up to the trunk), to laryngeal spasm and convulsions in severe cases (no loss of consciousness distinguishing these from tonic-clonic seizures); and
3. Addison's disease (AD) with clinical manifestations due to the combined deficiency of glucocorticoids, mineralocorticoids and androgens. The most frequent symptom is asthenia, and common manifestations include hypoglycaemia, hypotension and gastrointestinal dysfunction.

Other immune or non-immune mediated diseases, so called minor clinical manifestations, may be associated with APS-1 (Table 2).

In APS-2, the major clinical manifestations include:

1. Addison's disease, always present in these patients, with the same symptoms and signs as described earlier,
2. Thyroid autoimmune diseases (TAD), such as Graves' disease (usually present before AD) and chronic thyroiditis (usually simultaneously or after AD) and
3. Type 1 Diabetes mellitus (DM). As for APS-1, APS-2 may be associated with other minor autoimmune diseases (Table 3).

Incomplete APS-2 should be considered in two scenarios: (1) patients that present positive thyroid antibodies and/or ICA or GAD antibodies as well as AD; or (2) patients that present positive ACA/21-OH as well as TAD or type 1-DM. APS-3 is defined by the association of TAD with other autoimmune disease but not AD or CH (Table 4). This is the most common APS since TAD is the most frequent autoimmune diseases in the general population.

In 2001, Betterle proposed a new classification that distinguishes 4 subgroups of TAD related to disorders of four different main systems (Table 4). An incomplete APS-3 can be considered when patients present TAD associated with organ and non-organ specific autoantibodies and with no clinical evidence of other autoimmune disease.

Clinical manifestations associated with APS-4 are miscellaneous combinations of clinical presentations associating endocrine and non-endocrine autoimmune

Table 1. APS-1 Major Clinical Manifestations Description and Prevalence [1].

Chronic candidiasis	Mucocutaneous candidiasis		18–100%
	Chronic oesophagitis, oesophagus stenosis		
Chronic hypo-parathyroidism	Neuromuscular	Paresthesias, tetany, irritability, depression, psychosis, cerebral calcifications and intracranial hypertension with papilloedema	76–100%
	Cardiovascular	Prolonged QT interval on ECG, arrhythmias and hypotension	
	Gastrointestinal	Intestinal cramps, malabsorption and steatorrhoea	
	Cutaneous	Dry skin, thick hair and nail dystrophy	
Addison's disease	Constitutional symptoms	Asthenia, fatigue, weakness, weight loss and anorexia	22–100%
	Gastrointestinal	Nausea, vomiting, abdominal pain and diarrhoea (sometimes alternating with constipation)	
	Cardiovascular	Orthostatic hypotension and syncope	
	Metabolic	Hypoglycaemia	
	Cutaneous	Skin hyperpigmentation	
	Neuro-psychiatric	Depression, psychosis, confusion, delirium, stupor and pseudotumour cerebri	
	Sexual	Axilary and pubic hair decreased in women, reduced libido and erectile dysfunction	

Table 2. APS-1 Minor Clinical Manifestations and Prevalences [1].

Endocrinopathies	Hypergonadotropic hypogonadism (24–60%), thyroid autoimmune diseases (4–36%), type 1 diabetes mellitus (0–12%), lymphocytic hypophysitis (7%)
Gastrointestinal autoimmune diseases	Atrophic gastritis (13–27%), pernicious anaemia (0–15%), coeliac disease, autoimmune hepatitis (5–31%), malabsortion (18–22%)
Cutaneous autoimmune diseases	Vitiligo (0–25%), alopecia areata (13–72%)
Systemic autoimmune diseases	Sjögren's syndrome; rheumatoid arthritis
Immunological alterations	IgA deficiency, polyclonal hypergammaglobulinaemia
Others	Ectodermal dystrophy (10–52%); asplenia (very rare); malignant neoplasias (1–7%); calcification of basal ganglia, membrane tympani and sublenticular cataract; vasculitis; nephrocalcinosis.

Table 3. APS-2 Clinical Manifestations and Prevalence [1].

Major	Addison's disease	Same as for APS-1 (Table 1).	100%
	Thyroid autoimmune diseases	Graves' disease, Hashimoto's thyroiditis, idiopathic myxoedema, asymptomatic thyroiditis, endocrine ophtalmopathy, pretibial myxoedema	69–82%
	Type 1 Diabetes mellitus		30–52%
Minor	Hypergonadotropic hypogonadism (4–9%), vitiligo (4,5–11%), alopecia (1–4%), autoimmune hepatitis (4%), chronic atrophic gastritis (11%), pernicious anaemia (1–4,5%), hypophysitis, neoplasias (2%)		

Table 4. APS-3 Clinical Manifestations [1].

Thyroid autoimmune diseases			
Hashimoto's thyroiditis Idiopathic myxoedema Endocrine exophthalmos Graves' disease Asymptomatic thyroiditis			
3A Endocrine diseases	3B Gastrointestinal apparatus	3C Skin/ haematopoietic/ nervous system	3D Connective tissue diseases/vasculitis
Type 1 DM Hirata's syndrome Premature ovarian failure Lymphocytic hypophysitis Neurohypophysitis	Atrophic gastritis Pernicious anaemia Coeliac disease Chronic inflammatory bowel diseases AIH Primary biliary cirrhosis Sclerosing cholangitis	Vitiligo Alopecia Autoimmune thrombocytopenia Autoimmune haemolytic anaemia Antiphospholipid syndrome Myasthenia gravis Stiff-man syndrome Multiple sclerosis	SLE Mixed connectivitis Rheumatoid arthritis Reactive arthritis Scleroderma Sjögren's syndrome Vasculitis

diseases not included in the previous groups. For example, AD associated with hypogonadism, chronic gastritis, etc, or type 1 DM with coeliac disease, Myasthenia gravis, etc.

3 Diagnostic criteria

Diagnosis is based on clinical criteria, since no specific laboratory test has been described to date. Hypoparathyroidism, Addison's disease or Diabetes mellitus with associated endocrine failure or malfunction can easily be detected by direct serum assays. But the proposed classification by Neufeld and Blizzard from 1980 is based on clinical criteria, describing four main syndromes (Table 5).

Table 5. Classification Criteria for APS. Adapted from [1].

APS-1	Chronic candidiasis, chronic hypoparathyroidism, Addison's disease (*at least two present*)
APS-2	Addison's disease (*always present*) *with* autoimmune thyroid disease *and/or* type 1 Diabetes mellitus
APS-3	Autoimmune thyroid disease *with* other autoimmune diseases (*excluding* Addison's disease *and/or* hypoparathyroidism)
APS-4	Other combinations not included in the previous groups

4 Diagnostic measurements for experts

The presence of immunological abnormalities or confirmed lymphocytic infiltration of the target-organ is not required for APS diagnosis. Although limited, there is a role for autoimmune and genetic tests. The presence of circulating, tissue-specific autoantibodies may be associated with or precede the clinical manifestations and serve as diagnostic markers — with the exception of ICA and/or GAD antibodies which seem to have low value for predicting type 1 DM. Several other autoantibodies are related to minor clinical manifestations as detailed in Table 6. Most of these tests cannot be performed on a routine basis. Non-organ specific autoantibodies are relatively common in patients with TAD, mostly common in APS-3 and are pivotal for the diagnosis of systemic autoimmune diseases such as SLE. Besides immunologic mechanisms, known genetic abnormalities or patterns are associated with APS. APS-1 is unique as a monogenic disease inherited as an autosomal recessive trait. The defective gene AIRE (Auto Immune Regulator) has been identified and is also the most representative mutation of all the APS. APS-2 has an autosomal dominant inheritance with incomplete penetration and correlates to different HLA alleles (increased frequency of HLA-DR3 and/or DR4). Genetic screening could be considered in high risk populations or close relatives of APS patients to allow early diagnosis and replacement treatment.

5 Requirements for family practitioners

The APS are very rare syndromes. For family practitioner, all that should be required is the identification of the main clinical manifestations and awareness of possible associations that should raise the suspicion of an APS for appropriate evaluation, follow up and reference to experts or differentiated centres. This knowledge will allow an adjusted approach and the identification of APS in a pre or subclini-

Table 6. APS and antibodies — adapted from [1].

APS	Disease	Autoantibody to
APS-1	CH	Parathyroid antibodies (11–38% patients), calcium-sensing receptors*
	AD	Adrenal cortex (ACA) (84% of patients show positivity for at least one of these autoantibodies): 21-OH*; P450 side chain cleavage (SCC) enzyme; 17α-OH
	Hypogonadism	Steroid-producing cells antibodies (StCA): 17α-OH and P450scc
	TAD	Peroxidase, thyroglobulin* (positive in most patients)
	AIH	Anti-LKM*, P450-IA2, P450-2A6
	Alopecia	Tyrosin
	Vitiligo	Melanocyte (complement-fixing), aromatic aminoacid decarboxylase (AADC), transcription factors Sox9 and Sox10* (63% of patients)
	Type 1 DM	Islet cell (ICA), glutamic acid decarboxylase (GAD), second islet antigen (IA-2) – high frequency in APS-1 patients but low correlation to type 1-DM
	Atrophic gastritis	Parietal cells*, intrinsic factor (if also pernicious anaemia), H+K+-ATPase
	Malabsorption	Tryptophan hydroxylase* (48% of patients) Endomysium (related to coeliac disease)
	Hypophysitis	Anti-pituitary (rare), prolactin-secreting cells
APS-2	AD	ACA/21-OH (91% patients)
	Type 1 DM	High frequency of positive ICA, GAD or IA2 Abs
	Minor AID	Less frequent, usually associated to positive Abs
* The major autoantibodies related to clinical findings		

cal phase. When a child presents CC that can be the first manifestation of APS-1, it is important to maintain close observation and re-evaluation. Usually, endoscopic evaluations are not necessary and should be reserved for selected cases. The subsequent presence of symptomatic or asymptomatic hypocalcaemia may identify CH. In the initial evaluation, it is necessary to evaluate calcium serum levels, phosphate, parathyroid hormone (PTH) and 24 h urine calcium and phosphate. PTH serum levels should be low or undetectable with calcium serum levels low and phosphate levels high. Hypercalciuria is associated with low phosphate urinary elimination. About 50 % of APS-1 patients will present all three clinical criteria: CC, CH and AD. Routine laboratory abnormalities in AD may be absent in the early stages. In APS-1, as in APS-2, AD is typically associated with hyponatraemia, hypochloraemia, hyperkalaemia and reduced plasma osmolarity. Other possible findings are hypoglycaemia, mild eosinophilia with lymphocytosis and micro or macrocytic anaemia. For the diagnosis of AD, morning levels of ACTH are increased and cortisol reduced. Reduced levels of aldosterone (with increased plasma renin activity) and dehydroepiandrosterone are also present. The evaluation of TAD, in both APS2 and 3, implies determination of TSH, free T3 and T4 levels, anti-thyroid antibodies and thyroid ultrasound. Practitioners should also be aware of minor clinical manifestations.

6 Follow up

Life-long monitoring is important for all diagnosed patients. Persistent Candida infection can lead to epithelial carcinoma of the oral mucosa, tongue or oesophagus. In particular in APS-1, close follow-up of children with CC is mandatory for the early recognition of other features and for the risk of epithelial carcinoma.

All patients should be screened for a broad range of autoantibodies and regular re-evaluation should be considered (every 1–2 years). Special emphasis should be given to ACA/21-OH (diagnostic marker for AD) and thyroid antibodies (those with positive results should be monitored for the development of TAD). Considering APS-2, incomplete forms should be screened for subclinical diseases.

7 Management

Hormonal replacement therapy is mandatory in primary hypothyroidism and adrenal insufficiency. In APS-1, the standard treatment for CC is periodic administration of itraconazol, usually more effective for nail infections than mucosal infections. Insulin should be administered for type 1 DM. For CH, treatment is based on long term administration of calcium and vitamin D (already hydroxylated forms) *per os*. For acute treatment of symptomatic hypocalcaemia, intravenous calcium administration is required on an emergency basis with continuous electrocardiographic monitoring.

8 Diagnostic tests

Regarding the clinical manifestations of gland insufficiency, routine laboratory evaluation aims at assessing endocrine organ function. As mentioned earlier, in the presence of those clinical and laboratory findings, diagnosis is based on clinical criteria alone.

Diagnosis of an autoimmune disease includes the demonstration of serum autoantibodies and/or *in vitro* cell-mediated events, or the demonstration of lympho-monocyte infiltration in the target organ. But those findings are not required for diagnostic purposes.

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