

POLYGLANDULAR AUTOIMMUNE SYNDROMES (PGA)

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Autoimmunity represents the most common cause of endocrine gland dysfunction.

The spectrum of autoimmune endocrine disorders is broad, the process affecting almost all endocrine glands.

A main feature of autoimmune endocrine diseases is their tendency to associate with each other and with other organ-specific autoimmune disorders.¹

Definition of PGA

PGA involve multiple endocrine gland insufficiencies (minimum two), being frequently associated with diseases of non-endocrine organs,

and occur in individual patients and their families.^{1,2}

The autoimmune endocrine associations recognise more generics: autoimmune polyglandular syndromes (APS), autoimmune polyendocrine disease (APD), polyglandular failure syndromes (PFS), and polyglandular deficiency syndromes (PDS).

In the association of multiple endocrine diseases, one or more entities may present a sub-clinical form.

Classification of PGA and its components is presented in Tables 1 and 2.

Besides the classical entities of patients with Addison's disease, there are groups – sometimes referred to as autoimmune polyglandular syndrome

Table 1. The components of PGA³

PGA Type I	Major components	PGA Type II
<ul style="list-style-type: none"> • Chronic mucocutaneous candidiasis (CMC) • Hypoparathyroidism • Autoimmune adrenalitis (AA) 		<ul style="list-style-type: none"> Autoimmune adrenalitis (AA) Autoimmune thyroid diseases (AITD) Insulin-dependent diabetes mellitus (IDDM) Gonadal failure
	Other endocrinopathies	
<ul style="list-style-type: none"> IDDM Ovarian failure Testicular failure Hypothyroidism 		<ul style="list-style-type: none"> Lymphocytic thyroiditis Isolated ACTH or LH/FSH deficiency Lymphocytic infundibulo-neurohypophysitis
	Other features	
<ul style="list-style-type: none"> Vitiligo Alopecia Pernicious anaemia Enamel hypoplasia Tympanic membrane calcification Nail dystrophy Keratopathy Hepatitis Malabsorption 		<ul style="list-style-type: none"> Vitiligo Alopecia Pernicious anaemia Celiac disease Myasthenia gravis

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type III – in which a direct association of thyroiditis and IDDM is found in the absence of autoimmune adrenalitis (Table 2, Fig. 1).

Table 2. Classification of PGA⁴

- I. Candidiasis, hypoparathyroidism, Addison's disease (2 or 3 present)
- II. Addison's disease and thyroid autoimmune disease and/or IDDM
- III.
 - A. Thyroid autoimmune disease and IDDM
 - B. Thyroid autoimmune disease and pernicious anaemia
 - C. Thyroid autoimmune disease and vitiligo and/or alopecia and/or other organ-specific autoimmune diseases not falling into the above categories.

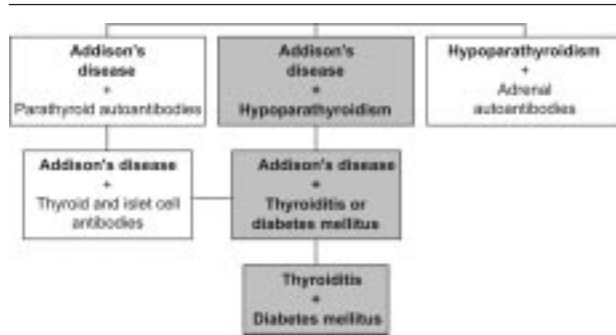


Figure 1. The three major clinical categories of PGA and variants⁵

Other associated diseases (endocrine and non-endocrine) are presented in Table 3.

Table 3. Other diseases associated with PGA

Other endocrine disorders	Non-endocrine disorders
Graves' disease	Mucocutaneous candidiasis
Ovarian failure	Pernicious anaemia
Testicular failure	Vitiligo
Hypophysitis	Alopecia
-	Chronic active hepatitis
-	Malabsorption

Table 4. Characteristics of the type I and II PGA⁶

Characteristic	PGA type I	PGA type II
<i>Incidence</i>	rare	more common
<i>Female / male ratio</i>	1.4 / 1.0	1.8 / 1.0
<i>Age at onset</i>	childhood	adult life
<i>Inheritance Pattern</i>	autosomal recessive pattern	autosomal dominant with incomplete penetrance
<i>HLA types</i>	A28, A3	primarily B8, DW3, DR3, DR4 and others in special cases
Clinical manifestations (% involved)		
Addison's disease	60 - 67	100
AITD	10 - 11	69
Pernicious anaemia	13 - 15	↑ 1
IDDM	2 - 4	52
Gonadal failure	45	3.5
Hypoparathyroidism	82 - 89	not seen
Vitiligo	4 - 9	5 - 50
CMC	73 - 78	not seen
Chronic active hepatitis	11 - 13	not seen
Alopecia	26 - 32	not seen
Malabsorption	22 - 24	not seen
Celiac disease and myasthenia gravis	not seen	uncertain incidence

PGA I and PGA II present distinct characteristics regarding:

- the incidence
- the F/M ratio
- the age at onset
- the mode of inheritance and HLA types
- the clinical picture

Features of PGA syndromes

The main features of polyglandular autoimmune syndromes are presented in Table 4.

Pathophysiology

The autoimmune nature of these syndromes is based on the following observations:

- the affected organs present a chronic inflammatory infiltrate (composed mainly of lymphocytes);
- some entities are associated with immune response genes encoded by class II loci of the HLA complex;
- in the serum of patients are present antibodies (Abs) against tissue-specific antigens;
- cellular immunity defects were also observed

The main factors implicated in autoimmune endocrine disease are represented by T lymphocytes and antibodies elaborated by B lymphocytes, with a specific recognition of target antigens.^{2,7,8}

The antibodies may arise in a primary fashion (breakdown of normal immunologic tolerance), by immunization with an environmental agent (molecular mimicry of a self antigen), or during a secondary immune response (after the release from damaged glands of intracellular antigens, normally "sequestered" from the immune system).⁹

The antibodies identified in PGA react with organ-

Table 5. Organ-specific antigens involved in PGA

Target organ	Enzymes	Receptors	Secreted cell products
Islet cell	Glutamic acid decarboxylase	Insulin glucose transporter	Insulin
Proinsulin			
Thyroid	Thyroid peroxidase	TSH	Thyroglobulin
Adrenal	21 OH		
17 OH	ACTH	-	
Gonad	17 OH	Gonadotropins	-
Gastric parietal cell	H ⁺ /K ⁺ ATP-ase	-	Intrinsic factor

specific antigens (Table 5) and represent important diagnostic indicators and predictive markers for the future disease. Their pathogenic relevance remains more or less unclarified.

T lymphocytes may recognise peptide fragments of auto antigens in special conditions (only if the peptides are presented on the surface of another cell by HLA molecules). T helper cells (CD4) react with antigenic peptides derived from extra cellular fluid bound by class II HLA molecules on the surface of antigen-presenting cells. In response, T helper cells elaborate different lymphokines, leading to an autoimmune response to the antigen.

Cytotoxic cells (CD8) react with peptides bound by class I HLA molecules, present on the surface of almost all cells. Both types of T cells (helper, cytotoxic) are able to destroy target cells by specific pathways. The types of immunologic tissue injury are very complex.

Genetics and role of environment

Both genetic and environmental factors contribute to the loss of immune self tolerance.

The susceptibility to most autoimmune diseases has a significant genetic component, demonstrated also by familial studies. The inheritance pattern of autoimmune disorders is very complex. The most clearly established genetic association for predisposition to autoimmune diseases is the genotype of the MHC.

The environmental factors may have an important influence on the development of autoimmune diseases, but the exposure to environmental pathogens does not always result in disease.^{10,11} If the genetic factors are likely to operate most strongly in children with PGA, the environmental factors will tend to operate most strongly in later life.

The natural history of endocrine autoimmunity

The natural history of autoimmune disorders includes several stages (Fig. 2):

- in people with a genetic predisposition, an unknown precipitating event starts the autoimmune process;

- the early process manifests itself by antibody

production; sometimes it may arrest at this stage;

- progressive disease associated with secondary responses against antigens released by damaged tissue is detectable by minimal biochemical abnormalities;

- during the sub-clinical phase of organic failure the organ function loss is not total;

- the organ function loss may progress to clinically overt disease.^{1,12}

**Figure 2.** Natural history of endocrine autoimmunity

Particular aspects of the most important endocrine disorders

PGA I (Autoimmune polyendocrinopathy – Candidiasis – Ectodermal dystrophy) is characterised by the triad: chronic mucocutaneous candidiasis (CMC), autoimmune hypoparathyroidism and autoimmune adrenalitis (AA).¹³ The chronology of main components is very exact.

CMC frequently precedes both endocrinopathies. Hypoparathyroidism develops in the first decade, followed by AA in about 2 years. The patients may be affected by a third endocrinopathy or non-endocrine disorder (AITD, IDDM, hypogonadism, pernicious anaemia).

The adrenal antigens are represented by several enzymes of the cytochrome P 450 family, including 21-hydroxylase, 17-hydroxylase and side chain cleavage enzyme (P450 scc). The parathyroid antigen is not well characterized.

The presence of CMC suggests that a defect in T-

cell function may be essential for the pathogenesis of this syndrome.¹

Regarding the epidemiology of PGA I, the three main entities appear during the first 20 years of life. The accompanying diseases develop until the fifth decade.

The earlier the first component appears, the more likely is that multiple components will develop. Cases with late manifestations tend to develop fewer components.

PGA I may induce various clinical manifestation in childhood .

CMC affects nails, dermis and mucous membranes. The clinical course is progressive with remissions. Sometimes the gastrointestinal involvement may become severe.¹³ Hypoparathyroidism in children tends to be sometimes dangerous (laryngospasm, seizures). During the neonatal period it is necessary to exclude Di George syndrome (absence, maldescent or maldevelopment) of the parathyroid glands and variable degrees of thymic hypoplasia).^{1,14,15}

PGA II represents the most common form of autoimmune endocrinopathy (approx. 14 – 20 cases/1000,000 inhabitants). It associates in the same individual two or more of the following diseases: AA, AITD, IDDM, primary hypogonadism, myasthenia gravis and celiac disease. The time course of the development of organ-specific autoimmunity is indefinite and imposes re-evaluation of patients and their families repeatedly over time.

The syndrome may be more difficult to detect before the onset of clinical polyglandular diseases. In 50 % of cases it is heralded by adrenalitis.^{8,15}

The onset of the syndrome appears in the third and fourth decades of life, and its character is a familial one. About 20 years can elapse before the manifestation of polyglandular involvement.

The auto antigens are heterogeneous, being often represented by hormones (insulin) or enzymes (thyroid peroxidase, 21-hydroxylase, glutamic acid decarboxylase and carboxypeptidase H 29, the last two in IDDM).

The association of AA, IDDM and thyroiditis (Schmidt's syndrome) is quite often seen in clinic. IDDM and Hashimoto's thyroiditis develop at an average of 7 years after adrenal insufficiency.

Patients with Schmidt's syndrome have thyroid autoantibodies (with a predictive role for thyroid failure) and islet cells autoantibodies (sometimes transitory and with a predictive role for future insulin requirement).

It may be also associated with ovarian failure, related to a distinct type of auto antibody against

common antigens for multiple steroid-producing cells (adrenal cortex, theca interna, corpus luteum, Leydig cells, placenta).¹¹

The different autoimmune disorders observed in patients with AA are presented in Table. 6.

Table 6. Other autoimmune disorders in patients with AA (419 cases)¹¹

Autoimmune disorder	Incidence (%)
IDDM	10
Hyperthyroidism	8
Thyroiditis	9
Hypogonadism	16
Hypoparathyroidism	5
Pernicious anaemia	4

The most important immunological aspect of AA is represented by the occurrence of specific antibodies reacting with all three zones of adrenal cortex. The presence of autoantibodies seems to precede the development of overt disease by several years. From all the subjects presenting autoantibodies, 16-40 % / year may develop adrenalitis.^{7,8,12,15,16}

The deficiencies of mineralo and glucocorticoids usually arise simultaneously, but their onset may be dissociated by up to five years. The first sign of the disease is represented by high plasma renin activity (PRA) associated with normal or low serum aldosterone. After a time the response of cortical to ACTH is blunted and finally ACTH increases and cortisol values decrease.¹² The patients with isolated AA may present in serum an increased prevalence of different antibodies (against thyroid, parathyroid, islet cells, etc.).

The thyroid autoimmune diseases, frequently observed comprise autoimmune hyperthyroidism and various entities of autoimmune thyroiditis. The autoantibodies detected in AITD are directed against: thyroglobulin, thyroid peroxidase, TSH receptor and thyroid hormones (thyroxine and triiodothyronine). Cellular disorders regarding mainly suppressor T lymphocytes are also present.⁹

Diagnostic protocols

The first investigations regard the serum screening for different antibodies (against adrenal, islet cells, thyroid, gonad, gastric parietal cells, etc). Soon after, the antibody positive individuals need assessments of end-organ functionality (tropic hormones, blood glucose, the parameters of phospho-calcium metabolism, haematological investigations, etc, performed annually in asymptomatic cases).

In patients with overt autoimmune diseases (endocrine, non-endocrine) complex and specific determinations are needed.

Differential diagnosis may sometimes be difficult.

The most serious pitfall in the diagnosis of PGA is to confuse a form of the syndrome with hypopituitarism.

Other aspects regard the correct diagnosis of primary endocrine failures of non-autoimmune origin, POEMS syndrome and other rare diseases (hemochromatosis, myotonic dystrophy, etc).

Therapy

For a successful management of PGA syndromes a precocious diagnosis is necessary.

The treatment of organ failures is a substitutive one.¹⁷

The treatment implications of polyglandular insufficiencies are not yet well established.

The management of AA is the classical one, with the use of increased glucocorticoid doses at times of acute stress (also in cases with the asymptomatic disease who have biochemical evidences of AA) and a proper recognition and therapy of emergencies.

In AA associated with ovarian failure, sex steroid replacement therapy can prevent severe osteoporosis.

The association of AA and hypoparathyroidism may pose complex problems. The treatment of IDDM and AITD imposes special rules and a careful monitoring.

Prognosis

In PGA type II the rates of morbidity and mortality are not negligible.

The occurrence of IDDM does not carry a satisfactory prognosis because of its complications (vascular, metabolic, etc.).

The prognosis of AA is improved by an attentive surveillance for failure of previously uninvolved glands.

The prognosis of patients is also influenced by age and co-morbidity.

CONCLUSIONS

- PGA syndromes are quite well-outlined entities,

that can be detected at an asymptomatic stage by screening of high-risk individuals.

- Specific antibodies have diagnostic and prognostic value in symptomatic and asymptomatic cases.

- The follow up of PGA patients is as important as the therapy.

- Genetic counselling and the supervision of patients' families are needful.

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Self-Assessment Examination

POLYGLANDULAR AUTOIMMUNE SYNDROMES (PGA)

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- Some features of PGA are represented by:
 - multiple endocrine gland involvement
 - mainly endocrine gland hypo function
 - mainly endocrine gland hyper function
 - only a clinical presentation of the diseases
 - a sub-clinical presentation of the diseases also possible
- The major components of PGA I are the following:
 - hypoparathyroidism
 - IDDM
 - chronic candidiasis
 - AA
- Some of the most common components of PGA II are represented by:
 - AITD
 - hypoparathyroidism
 - IDDM
 - auto-immune hypophysitis
- The differences between PGA I and PGA II are related to:
 - the incidence
 - the associations with other autoimmune non-endocrine diseases
 - the age of onset
 - the clinical picture
- The Abs involved in PGA are:
 - directly harmful to the tissues
 - reacting with organ-specific antigens
 - useful for the positive diagnosis
 - without predictive value for the future disease
- The organ-specific antigens involved in PGA are represented by:
 - enzymes
 - hormonal receptors
 - hormones
 - other peptides
- For the natural history of an autoimmune endocrine disease, the following facts are valid:
 - a genetic predisposition for the disease
 - an elucidated role of cellular autoimmunity
 - an occurrence in the evolution of the disease of a sub-clinical phase
 - an obligatory progression of the sub-clinical phase to clinically overt disease
- In cases with PGA I:
 - candidiasis is the first occurring disease
 - the chronology of main components of the syndrome is not very exactly
 - the syndrome affects mainly children
 - other autoimmune diseases are commonly associated
- PGA II has the following traits:
 - is the most common form of polyendocrinopathy
 - AA, AITD and IDDM are frequent associations
 - the syndrome is heralded by IDDM
 - the time course for the development of the syndrome is clearly definite
- In AA:
 - the specific antibodies react only with some zones of adrenal cortex
 - the hormonal deficiencies arise customly dissociated
 - the first hormonal sign of the disease is: high plasma renin activity (PRA) and normal or low aldosterone
 - the first hormonal sign of the disease is represented by high values of serum ACTH.

To complete the examination for CME evaluation turn to page 96 for instructions and the response form.

Correct answers for CME: Sepsis (II). (TMJ 2003;2:185-9): 1-abd; 2-ce; 3-d; 4-ce; 5-abd; 6-bd; 7-a; 8-abce; 9-de; 10-bde; 11-cd; 12-abc.