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Review

AUTOIMMUNE POLYGLANDULAR SYNDROMES: INCOMPLETE ASSOCIATIONS, DIFFICULTIES OF DIAGNOSIS MAKING AND PATIENTS' FOLLOW-UP

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Abstract

Autoimmune diseases, both endocrine and somatic, as well as their associations leading to high disability rates, especially in children and adolescents, present important challenges of modern Endocrinology. There is a large body of evidence indicating the association of specific autoimmune diseases of both endocrine and somatic genesis, which form several types of autoimmune polyglandular syndromes.

The classification of autoimmune polyglandular syndromes suggests associations of definite autoimmune diseases, whereas rare associations are not taken into account and this latter creates diagnostic difficulties for the clinical endocrinologists. Moreover, it is worth mentioning that there are many rare associations, which are described to fulfill the missing parts of classification and raise the need of more general and comprehensive classification.

In this article two cases are described, one of which emphasizes the significance and effectiveness of screening examinations for the target groups. The other case explores difficulties faced by doctors, because of scanty or lacking clinical features upon diagnosis setting for autoimmune polyglandular syndromes. Moreover, the lack of clinical features makes doctors not always realize the exact diagnosis of patients and further follow-up. In the first case, the diagnosis was autoimmune polyglandular syndrome type 3. In the second case a patient that was admitted to Pediatric Endocrinology Department of "Muratsan" Hospital (Yerevan, Armenia) was suspected to have one of autoimmune polyglandular syndromes types. However, the precise diagnosis was not made properly, because of imperfection in both autoimmune polyglandular syndromes classification and certain genetic analyses in the laboratories of Armenia. Therefore, it is our point to draw special attention to any hormonal disturbance in mentioned groups of patients and to screen them for probable further autoimmune endocrine disorders annually. It is also worth mentioning that carrying out annual screening tests in children and adolescents with type 1 diabetes mellitus plays the most important role. These tests, undoubtedly, help to find out the disease at an early stage and, consequently, help in early treatment of autoimmune pathology of other endocrine organs. Moreover, it helps in setting the exact diagnosis of autoimmune polyglandular syndromes.

Keywords: autoimmune diseases, autoimmune polyglandular syndromes, autoimmunity, vitiligo, alopecia, autoimmune thyroiditis, Addison's disease, autoantibodies.

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Autoimmune polyglandular syndromes (APS) are one of the most interesting and actual problems in endocrinology and at the same time one of its unclear branches. Interestingly, it is not a mere endocrinology problem related to both pediatric endocrinologists and endocrinologists, who treat adults, but also an internal mixed – somatic and

glandular – pathology. The reason for this is the fact that it has many common edges with autoimmune somatic diseases not only of endocrine origin. Thus, it is an actual problem for both pediatricians and general therapists as well.

Numerous pathologies of endocrine system are described to be of autoimmune genesis: type 1 diabetes mellitus (DM); Grave's disease or diffuse toxic goiter (DTG); Hashimoto's thyroiditis also known as autoimmune thyroiditis (AIT); Addison's disease or chronic adrenal insufficiency (AD); hypoparathyroidism; hypophysitis, etc. Furthermore, there are many somatic autoimmune disorders such as celiac disease, autoimmune hepatitis, pernicious anemia (PA), *myasthenia gravis*, vitiligo, alopecia, etc.

Recent evidences show that in last decades there are more and more authors, who indicate the presence or association of more than one organ-specific autoimmune disease – both endocrine and somatic. Moreover, recently more and more specialists have begun to discuss the autoimmune polyendocrinopathies. The identification of circulating organ-specific autoantibodies provides the earliest and strongest evidence for the autoimmune pathogenesis of the above-mentioned pathologies. Perhaps, it is connected with the implementation and use of sensitive diagnostic tools, such as identification of autoimmune processes markers: autoantibodies against selective specific autoantigens.

However, the concept of polyglandular failure is not a new phenomenon. In 1853, Thomas Addison first described the adrenal failure (which was later called AD) in a patient with PA. In 1866, J. Oegle first described the association between DM and AD. However, it is worth mentioning that the adrenal insufficiency was due to tuberculosis, but not of autoimmune genesis [*Oegle J., 1866*]. Later, in 1910, J. Parkinson gave the first definition of a patient with coexisting diabetes and PA [*Parkinson J., 1910*]. In 1908, M. Claude and H. Gougerot suggested a common pathogenic point in polyglandular endocrinopathies [*Claude M., Gougerot H., 1908*]. In 1926, M. Schmidt diagnosed the association of adrenal insufficiency with thyroiditis [*Schmidt M., 1926*], and in 1964, C. Carpenter and co-workers reported the third often coexisting disease: type 1 DM; this latter association is called Carpenter's syndrome [*Carpenter C. et al., 1964*], although W. Gowen described the first case of association of type 1 DM, AD and AIT in 1932 [*Gowen W., 1932*].

In order to explain, why multiple organs are involved in APS, B. Tadmor and associates hypothesized that organs derived from the same embryonic germ layer share common specific antigens [*Tadmor B. et al., 1992*]. Therefore, this very hypothesis perhaps explains the pathogenesis of APS-3 (e.g., thyroid-gastric autoimmune syndrome, at which both tissues are derived from the endodermal layer). However, it does not explain the APS-2 pathogenesis, in which the adrenal cortex is of mesodermal genesis, but the thyroid and the pancreas are of endodermal origin. It is still unclear, why autoimmunity occurs against proteins of endocrine tissues and not in other organs of the same germ layer. Moreover, how the immune system selectively recognizes these autoantigens, and why multiple organs might be involved in the same individual on different occasions, – are still unsolved issues. Until now there have been continuing debates on these issues, and there have been proposed more mechanisms occurring. Nevertheless, all hypotheses fail to comprehensively explain the APS development and mechanisms [*Kahaly G., 2009*].

In 1956, the so-called Whitaker syndrome was added, which included 3 pathologies: hypoparathyroidism, hypocorticism and generalized candidiasis. The same triad was also called "candidias-endocrine syndrome". Association of candidiasis with endocrine disorders gives a clear understanding of the cell-immunity defect, not only of the humoral one. Later, in 1980, M. Neufeld and co-workers gave the first classification of polyglandular failure [*Neufeld M., Blizzard R., 1980; Neufeld M. et al., 1980*]. They distinguished 2 categories: APS type 1(APS-1) and APS type 2 (APS-2). In 2004, G. Eisenbarth and P. Gottlieb extended the discussion on the classification of these syndromes [*Eisenbarth G., Gottlieb P., 2004*]. Later an additional group – APS type 3 (APS-3) – was subsequently described, which, in contrast to APS-1 and APS-2, did not involve the adrenal insufficiency [*Neufeld M. et al., 1981*].

In 2003, C. Betterle and R. Zanchetta [*Betterle C., Zanchetta R., 2003*] published an article and introduced the modified classification of APS, which had the following features (Table).

Table.

Classification of the APS according to M. Neufeld (modified)

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

Modern generally accepted classification of APS appears to be more complicated than M. Neufeld and associates initially reported; it has the following concept:

1. APS-1 or Autoimmune Polyendocrinopathy-candidias-ectodermal dystrophy (APECED), which usually begins in childhood and is characterized by triad of the disorders: candidiasis of the skin and mucous membranes, autoimmune hypoparathyroidism and Addison's disease. At the same time, the presence of two of the mentioned disorders can be the base for diagnosis of APS-1, whereas the third disease can develop within the life span (*intra vitam)*. However, recently the AutoImmune Regulator (AIRE) gene has been found on chromosome 21, which regulates the autoimmunity in a human organism. The association of APS-1 with various mutations of the AIRE gene was proved [*Meyer G. et al., 2001*]. This gene expresses in many organs and tissues, predominantly in thymus [*Bjorses P. et al., 2000; Eisenbarth G., Gottlieb P., 2004; Peterson P. et al., 2004*]. Nowadays it is difficult, but reasonably possible to establish the AIRE mutations exactly in a patient with expected symptoms of the disease. The difficulty is connected with the laboratory analyses, which are not done in many countries. Nevertheless, it is also possible to separate DNA and perform this analysis in other countries for the final confirmation of APS-1 diagnosis. Undoubtedly, discovery of the mentioned gene might be considered a breakthrough in science and clinical diagnosis of APS-1.

However, not all APS types are connected with mutations of the selective gene, which can be found and genetically confirmed like APS-1.

2. APS-2 also includes 3 disorders and is diagnosed by the simultaneous presence of 2 of the following: primary adrenal insufficiency, autoimmune disorders of thyroid (DTG or AIT) and type 1 DM. These are the obligate disorders at APS-2. However, other associated autoimmune diseases, such as primary hypogonadism, myasthenia, celiac disease, vitiligo, alopecia, pernicious anemia, etc., were also described. Type 1 DM is seen in 50% of cases, thyroid diseases – in 70%, and AD – in 100%. Adrenal insufficiency can develop both at the onset and in 20 years after the manifestation of the mentioned disorders [*Salvatori R., 2005*]. Commonly, APS-2 is reported to be associated with human leukocyte antigen (HLA) alleles B8, Dw3, Dr3 and Dr4, DRB1\DQB1 [*Majeroni B., Patel P., 2007; Cailat-Zucman S., 2009; Fourati H. et al., 2011*].

3. APS-3 includes autoimmune disorders of 2 of any endocrine glands, except adrenals. Several authors consider APS-3 as the part of APS-2 from the point of pathogenesis and prevention. Others [*Dittmar M., Kahaly G., 2010*] also distinguish 3 subcategories of APS-3:

APS-3 type A – AIT with type 1 DM (also known as polyglandular autoimmune syndrome type 3 variant);

APS-3 type B – AIT with PA;

APS-3 type C – AIT with vitiligo and/or alopecia and/or other organ-specific autoimmune disease.

As obvious from above, AIT plays a major pathognomonic role in the manifestation and diagnosis setting of APS-2 and APS-3 [*Shimomura H. et al., 2003*]. AIT is one of the most wide spread autoimmune disorders of the thyroid gland. Its prevalence is 0.1-1.2% in pediatric population and 6-10% in females over 60 years old [*Matsuura N. et al., 1990*]. N. Amino and co-workers declared 1 from every 10-30 adult females to have AIT [*Amino*

N. et al., 1999]. Nevertheless, we should also emphasize that another term also exists – thyroid autoimmunity, which is not AIT yet, but is the presence of anti-thyroid autoantibodies: anti-thyroglobulin (Anti-TG) and anti-thyroid peroxidase (Anti-TPO) [*Pearce E. et al., 2003*]. The significance of these two autoantibodies is not the same. Anti-TPO is more specific and sensitive for thyroid autoimmunity [*Padberg S. et al., 2001; Kordonouri O. et al., 2005; Gonzales G., 2007*]. Approximately 10% of healthy women and 5.3% of healthy men were shown to have the Anti-TPO positivity [*Gonzales G. et al., 2007*]. Thus, they can be so called "healthy carriers" of autoantibodies. It is also worth mentioning that even if autoimmunity starts at the same time, the target organs might be destroyed with different latency periods. Furthermore, antibody positive individuals are considered to be at higher risk of developing clinical dysfunctions and will require to be further studied using specific functional/morphological tests (i.e., determination of thyroid hormones, thyroid stimulating hormone (TSH) and thyroid ultrasound examination in patients with antibodies to thyroid; oral glucose tolerance test in those with antibodies to pancreatic islets; or adrenocorticotropic hormone (ACTH) and cortisol test in those with antibodies to adrenal cortex).

It should be also kept in mind that in APS-3 when AIT is associated with type 1 DM, the beneficial disorder is mostly type 1 DM [*Kim E. et al., 2003*]: in majority of cases AIT develops after the manifestation of DM [*Umpierrez G. et al., 2003; Hunger-Battefeld W. et al., 2009; Villano M. et al., 2009*]. Consequently, it would be evidently correct to describe the APS-3 type A as an association of type 1 DM with AIT, and not *vice verse*.

Non-typical APS are sporadically reported, such as the patient with APS-1, who had candidiasis, hypoparathyroidism, AIT, autoimmune myocarditis, pulmonitis, atrophic gastritis and hyperchromic anemia. However, no signs, symptoms and laboratory findings of hypocorticism were found [*Rodionova E., Pilutik V., 2000*]. The same authors reported about another patient, who had generalized candidiasis, hypocorticism with frequent crises, atrophic gastritis, B12-deficient anemia, autoimmune hepatitis, without hypoparathyroidism. Moreover, M. Bahceci and colleagues described the association of APS-3 with common variable immunodeficiency in a patient with AIT, primary hypogonadism and growth hormone deficiency. Nevertheless, the patient did not have adrenal or parathyroid diseases [*Bahceci M. et al., 2004*]. Another rare case of APS-3 was reported in monozygotic twins, one of which also had autoimmune leukopenia [*Ugur-Altun B. et al., 2004*]. In addition, a case was presented about a patient from Japan; the subject had APS-3 with associated autoimmune hepatitis [*Oki K. et al., 2006*]. There was another report from Japan: about a rare case in 61-year-old woman with type 1 DM. This case was described as having associated AIT, PA and idiopathic thrombocytopenic purpura. HLA-DQ A10102, 0103 and DQ B1 0602, 0601 alleles were found in this patient, which are paradoxically described in the literature as type 1 DM protective alleles [*Noriko O. et al., 2006*]. Yet, another case was about a patient from Poland, who had von Willebrand syndrome with primary hypothyroidism, *myasthenia gravis* – as an APS-3 [*Lubinska M. et al., 2007*]. One more case was connected with a patient from Turkey with generalized vitiligo, alopecia *universalis* and AIT [*Turkoglu Z. et al., 2010*].

Rarely, growth hormone deficiency also may be a component of all APS, although it was reported more often with APS-1 and APS-2 [*Quintos J. et al., 2010*]. Very rare combinations of APS are described in association with ulcerative colitis, sclerosing cholangitis, and seronegative ocular myasthenia [*Briscoe N., Mezei M., 2009; Farkas K. et al., 2010*].

Many of the above mentioned authors suggest that in all APS-suspected cases complete hormonal observation and examination should be done regardless, whether it is APS-1, APS-2 or APS-3, because there are cases with symptoms and disorders non-typical for APS, and it is very difficult to distinguish the types of APS and to make the correct diagnosis.

Numerous unclear aspects of associated autoimmune endocrinopathies complicate the early diagnosis and targeted screening in patients with one autoimmune endocrinopathy. For example, the questions that do not have direct and definite answers yet: is any additional autoimmune disorder in type 1 diabetics considered as one of APS types? And do they need screening tests for other disorders during their whole life? If any autoimmune endocrinopathy and any somatic organ-specific autoimmune disease association might be consid-

ered APS-2 or APS-3?

Extremely rare autoimmune and non-autoimmune disorders should be also described in this article as well: immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and polyneuropathy, organomegaly, endocrinopathy, and monoclonal gammopathy, and skin changes (POEMS) syndromes. IPEX syndrome or the syndrome of X-linked polyendocrinopathy, immune dysfunction, and diarrhea (also known as XPID) is characterized as a rare recessive syndrome with aggressive autoimmunity, which results from mutation of the transcriptional activator, FoxP3, causing regulatory T-cell dysfunction. It manifests by enlargement of the secondary lymphoid organs, type 1 DM, eczema, food allergies, and infections. Persistent diarrhea in IPEX syndrome results from the secondary enteropathy. The diagnosis is confirmed by genetic analysis. Untreated IPEX syndrome is usually fatal in the first year of life: immunosuppressant drugs and/or bone marrow transplantation can prolong life, but are rarely curative.

The other rare syndrome is POEMS syndrome or Crow-Fukase Syndrome. It is a non-autoimmune polyglandular deficiency syndrome, which is probably caused by circulating immunoglobulins (Ig) resulting from plasma cell dyscrasia. Circulating cytokines, interleukins (IL) such as IL-1-β, IL-6, vascular endothelial growth factor, and tumor necrosis factor-α are also found to be increased in this syndrome. Clinical manifestations of the syndrome may include hepatomegaly, lymphadenopathy, hypogonadism, DM type 2, primary hypothyroidism, hyperparathyroidism, adrenal insufficiency, excess production of monoclonal IgA and IgG due to plasmacytomas and skin abnormalities (e.g., hyperpigmentation, dermal thickening, hirsutism, angiomas, hypertrichosis), etc. Treatment of this syndrome consists of chemotherapy and radiation therapy followed by autologous hematopoietic or stem cell transplantation. Five-year survival is about 60% [*Hogan W. et al., 2001; Rovira M. et al., 2001*].

Recognition of the above-mentioned syndromes is directed to early diagnosis and permits the initiation of specific therapy, as mentioned by researchers [*Eisenbarth G., Gottlieb P., 2004*]. For example, administration of a sulfhydryl-containing drug (such as methimazole) may be stopped, in case of Hirata's disease (insulin-autoimmune syndrome with insulin-autoantibody-induced hypoglycemia) [*Uchigata Y., Hirata Y., 1999*], or localized radiotherapy might be directed to a bone lesion or autologous bone marrow transplantation undertaken at POEMS syndrome [*Hogan W. et al., 2001; Rovira M. et al., 2001*].

Thus, as obvious from data above, the diagnosis of APS clinical manifestations is associated with great difficulties due to multiple types and diversity of autoimmune endocrine and somatic diseases. The below-mentioned cases from our clinical practice also support this statement. These cases are characterized, on the one hand, by manifestation of typical features of organ-specific autoimmune diseases, and, on the other hand, by some difficulties in the aspect of diagnosis and treatment of specified patients.

Clinical case 1. A 10-year-old female patient was admitted to Pediatric Endocrinology Department of "Muratsan" Hospital (Yerevan, Armenia); she presented with ketoacidosis and hyperglicemia. Type 1 DM was diagnosed and thyroid screening tests were performed. The onset of DM was characterized by euthyroid state; however, increased anti-TPO levels (190 *mU/L)* were observed. In a year, at the age of 11, alopecia *areata* was revealed on the left leg of the patient. The thyroid status still remained normal, but ultrasonography investigation revealed changes specific for thyroid autoimmunity; furthermore, significantly high anti-TPO levels (250 *mU/L*) were obtained. The patient was diagnosed for type 1 DM and alopecia *areata*. The child was under regular medical check-ups and underwent annual thyroid screening tests. In 2 years after DM onset, at the age of 12, the patient was additionally diagnosed to have autoimmune thyroiditis in the hypothyroid phase. The final diagnosis was set: APS-3, type 1 DM, AIT, hypothyroidism, alopecia *areata*. This is a case of APS easy and early diagnosis, if the target group for annual screening is clearly known, and suspected results are evidence-based, *viz*. by laboratory findings. It is also worth mentioning that screening tests of children and adolescents with type 1 DM play a very important role. These tests would definitely help to recognize the disease at an early stage and, consequently, help to cure autoimmune pathology of other endocrine organs. More-

over, it will help in making the exact diagnosis of APS in due time. However, there are some clinical cases, when the mentioned pathology displays are not clearly understood and suspected, likewise the second case from our practice.

CLINICAL CASE 2. An 8-year-old boy was admitted to Pediatric Endocrinology Department of "Muratsan" Hospital. At the age of 2 years the patient had infectious mononucleosis for several months followed by developed alopecia *areata* in the hairy part of the head and, a year later, – local vitiligo on the back. He has got treatment with Zn (tablets and creams), prednisolone and vitamins prescribed by dermatologist; the treatment was clinically helpful and effective (according to mother's opinion). However, after the treatment cessation clinical features of alopecia became vivid again. At the age of 5, the autoimmune thyroiditis in the phase of subclinical hypothyroidism was observed on the bases of elevated anti-TPO (>200 *mU/L*), TSH (8.6 *mU/L*), normal free thyroxine (fT4) (13 *mU/L*) and ultrasonography findings of AIT. Treatment with levothyroxine was prescribed and participation in annual screening for type 1 DM, hypocorticism and hypoparathyroidism. The patient was under follow-up for 3 years, no disorders were found.

The case described should draw your attention as an evidence of difficulties in APS diagnosis setting formulated as the questions below: whether this association can be diagnosed as APS-2 or APS-3 or "incomplete'' form of APS, or should we wait for the manifestation of other organ-specific APS-typical diseases for making diagnosis? P. Ameno and co-authors presented the combination of some autoimmune disorders in the association with vitiligo; however, they also did not represent the ultimate diagnostic criteria and the exact type of APS [*Ameno P. et al., 2006*].

The next question, which is still open, is: whether we should screen for earlier autoimmunity revealing of other glands and how long we should do that. Finally, the question is, whether there is cost-efficacy and preventive effectiveness of these screenings.

We should emphasize that recent years facilitated to improvement of knowledge on autoimmune disorders and their natural history, which gave an impulse for further study of all unclear and incomprehensible aspects of APS. Probably, this would allow to earlier identify patients with APS at the stage of potential risk or subclinical state and to prescribe hormonal replacement therapy not allowing development of the complete clinical manifestation of organ deficiency. Scientific implementation of new very sensitive and specific diagnostic tests for identification of definite target antigens and autoantibodies is of high significance. The discovery of the genetic mutations in patients with APS-1 will allow better understanding the mechanisms regulating immunological tolerance and developing new approaches for diagnosis setting and patient management.

The examples described above explore the problems faced by endocrinologists in their clinical practice, and these problems require further investigations and research. This kind of examination will allow the doctors to prescribe unified approach to research and examination of patients with any type of APS. It is of vital importance to recognize and treat the second or third complicating autoimmune disease, such as acute adrenal failure in a patient with type 1 DM or hypothyroidism in a subject with Addison's disease; moreover, it might be crucial, even life-saving.

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