

# Peculiarities of autoimmune polyglandular syndromes in children and adolescents

Giuseppina Zirilli, Simona Santucci, Chiara Cuzzupè, Domenico Corica, Elda Pitrolo, Giuseppina Salzano

Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy

**Summary.** *Background:* No reviews have specifically addressed, to now, whether autoimmune polyglandular syndromes (APSs) may have a peculiar epidemiology and phenotypical expression in pediatric age. *Objectives:* To review the most recent literature data about the specific epidemiological and clinical peculiarities of APSs in childhood and adolescence. *Design:* The main features of the different APSs in pediatric age were compared among them. *Conclusions:* 1) Among the different APSs, the one that is most typical of pediatric age is APS-1; 2) APS-1 is not characterized only by the classical triad (chronic moniliasis-hyposurrenism-hypoparathyroidism) and its clinical spectrum is enlarging over time; 3) APS-2 may have a different epidemiological and clinical expression according to two different nosological classifications. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** associations of autoimmune disorders, epidemiology, immunodeficiency, phenotypical expression

## List of abbreviations

AD: Addison's disease

APSs: autoimmune polyglandular syndromes

AITDs: autoimmune thyroid diseases

IPEX: immune dysfunction, polyendocrinopathy, X-linked

T1DM: type 1 diabetes mellitus

## Background

The autoimmune polyglandular syndromes (APSs) are characterized by the association of multiple autoimmune disorders and, in some cases, immunodeficiency (1). They include both monogenic illnesses, such as APS-1 and IPEX (immune dysfunction, polyendocrinopathy, X-linked) syndrome, as well as more complex genetic disorders, such as APS-2, APS-3 and APS-4.

The term "polyglandular" itself may be misleading, since some patients have multiple endocrine diseases, whereas others have many non-endocrine disorders (2). Some disorders, such as autoimmune thyroid diseases (AITDs) and type 1 diabetes mellitus (T1DM),

occur very often in all APSs, whilst other disorders, such as Addison's disease (AD) and myasthenia gravis are much more infrequent (1). In patients at risk for APSs, who have a single autoimmune disease, the prevalence of other autoimmune disorders is 30 to 50 times more elevated than in the general population (3). It has been estimated that one fourth of individuals with one autoimmune illness will develop another one throughout their lives (4).

APSs may occur at any age, with a different epidemiology between APS-1 and the other forms: whereas APS-1 is more common in childhood, APS-2 occurs most commonly in patients 30 to 40 years of age (5). However, to the best of our knowledge, no reviews have specifically addressed, to now, this interesting point, i.e. whether APSs may have a peculiar epidemiology and phenotypical expression in pediatric age.

Aim of this commentary is to review the most recent literature data concerning the specific epidemiological and clinical peculiarities of APSs in childhood and adolescence.

### *Peculiarities of APS-1 in childhood*

APS-1, also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, is a rare autosomal recessive monogenic disorder caused by mutations in the autoimmune regulator (AIRE) gene (6-8). More than 60 different mutations of this gene had been reported until 2012 (9, 10), but their number is progressively increasing over time (11). Some specific mutations are described to be associated with the geographical distribution of patients (10, 11), thus suggesting a potential founder effect (9). This might explain why APS-1 occurs worldwide, but its prevalence is distinctly higher among genetically isolated ethnic groups and particularly among Finnish (6), Sardinian (12), and Iranian Jewish populations (13).

It is a T-cell mediated disease with increased frequencies of CD8+ effector and reduction of FoxP3+T regulatory cells. In addition, APECED patients show a significant alteration of the B-cell phenotype and a dysregulation of B-cell function involving peripheral innate immune mechanisms; such alterations become more evident with increasing disease duration (14).

Clinical picture of APECED syndrome is mainly characterized by the classic triad: chronic mucocuta-

neous candidiasis, hypoparathyroidism and AD. These are the most common components of this syndrome, two of which are required for diagnosis (diagnostic dyad). Apart from these classic manifestations, however, many other endocrine and non-endocrine autoimmune disorders may occur in this condition, whose clinical spectrum has been reported to be progressively enlarging over time (15). The novel autoimmune disorders that have been described during the last years in individuals with APECED syndrome are: interstitial lung disease (16, 17), chronic inflammatory demyelinating polyneuropathy (18) and gastrointestinal dysfunction (19). For each of them the respective autoantigens and autoantibodies have been also identified (19-21).

Table 1 summarizes the main features of APS-1, APS-2, as defined according to the most recent nosological classification (1,2) and IPEX syndrome.

### *Peculiarities of APS-2 in childhood*

This autoimmune polyendocrine syndrome may be defined according to two different nosological classification.

According to the original classification of Neufeld and Blizzard (22), this condition is characterized by

**Table 1.** Epidemiological, genotypical and phenotypical peculiarities of autoimmune polyendocrine syndromes (APSs) as defined according to a recent nosological classification (References 1 and 2)

Features	APS-1	APS-2	IPEX syndrome °
<b>Prevalence</b>	Rare	Common	Very rare
<b>Preferential age at clinical onset</b>	Infancy	Adolescence and childhood	Neonatal period
<b>Inheritance</b>	Monogenic	Polygenic	Monogenic
<b>HLA genotype</b>	No association	DQ2 and DQ8	No association
<b>Common phenotype</b>	Candidiasis, hyposurrealism, hypoparathyroidism	Thyropathies, diabetes, hyposurrealism, celiac disease	Immunodeficiency, malabsorption, diabetes, dermatitis
<b>Other manifestations</b>	Malabsorption, Vitiligo, polyneuropathy, lung disease, gastrointestinal dysfunction,	Vitiligo, pernicious anemia, myasthenia gravis, alopecia others	Diabetes, dermatitis
<b>Clinical expressivity</b>	Very severe	Severe	Often fatal

°Immune dysfunction, polyendocrinopathy, enteropathy, X-linked

the mandatory presence of AD (100% of cases), which may be associated with either AITDs (Schmidt's syndrome) or T1DM (Carpenter's syndrome). The association with AITDs (69-82% of cases) is more frequent than that with T1DM (30-52% of cases) (23). The association with other autoimmune disorders (Table 2) is much less frequent and, however, non-mandatory.

According to the same classification (22), APS-2 is a specific clinical entity, which differs from APS-3 and APS-4 and is very rare: 1.4-2.0/100000 inhabitants (23). APS-2 may occur at any age and in both sexes, although it is especially common in middle-aged women and very infrequent in childhood (23).

APS3 is another clinical entity, which is characterized by the mandatory presence of AITDs (22). Other less frequent autoimmune disorders are: T1DM (APS3a), atrophic gastritis and pernicious anemia (APS3b), vitiligo, alopecia and myasthenia gravis (APS3c). AD and hypoparathyroidism are absent by definition (23). This condition would be less rare than APS-2 and it may present even in pediatric age (23).

According to the same classification of Neufeld and Blizzard (22), APS-4 is a further and very rare syndrome, that is characterized by the combination of autoimmune disorders not falling into APS-1 and APS-3 (chronic candidiasis, hypoparathyroidism, AITDs and T1DM). AD is a mandatory component of APS-4 and a positivity of autoantibodies against adrenal cortex/21-hydroxylase is absolutely required

for diagnosis (23). In individuals with suspicious APS-4 it is also important to exclude the coexistence of chronic moniliasis and/or signs of latent hypocalcemia, in order to exclude the possibility of a subclinical APS-1 (23).

According to another and more recent classification, which has been diffusely adopted in the last years (1, 2, 24-26), APS-2, APS-3 and APS-4 should not be considered as separate entities and could be included in the context of a single syndrome, which has been named as APS-2 (1, 2, 24-26). According to this recent view, APS-2 is the most frequent polyglandular syndrome (incidence 1-2:10000/year), that occurs more often in females (ratio 3:1) and may present from childhood to adulthood (25). Its inheritance is polygenic, with genes on chromosome 6 playing a predominant role (1). AITDs represent the most frequent clinical component of this condition (70-75%), followed by T1DM (50-60%), AD (40%) and other autoimmune disorders: celiac disease, vitiligo, pernicious anemia, myasthenia gravis and alopecia. Individual comorbidities may manifest even many years later, which reinforces the necessity of a widespread knowledge of this syndrome (1). This is particularly important considering that also first-degree relatives of children with APS-2 are at high risk of autoimmune diseases (1). In the light of all these considerations and the relatively high frequency of APS-2, it is important to recommend that children with AITDs or T1DM or AD or

**Table 2.** Epidemiological and phenotypical peculiarities of autoimmune polyendocrine syndromes (APSs) type 2, 3 and 4, as defined according to the classic classification of Neufeld and Blizzard (Reference 22)

Features	APS-2	APS-3	APS-4
<b>Prevalence</b>	Very rare	Common	Very rare
<b>Preferential age of clinical onset</b>	Middle age	Adolescence and early adulthood	From childhood to adulthood
<b>Inheritance</b>	HLA mutations	HLA mutations	HLA mutations
<b>Mandatory component</b>	Addison's disease	Thyropathy	Addison's disease
<b>Excluded component</b>	-----	Addison's disease and hypoparathyroidism	-----
<b>Minor autoimmune disorders</b> °	Infrequent	Common	Very common

° Vitiligo, alopecia, atrophic gastritis, pernicious anemia, hypophysitis

celiac disease are periodically monitored for other autoimmune disorders, although the optimal screening interval is not defined.

The main features of APS-2, APS-3 and APS-4, as defined according to the nosological classification of Neufeld and Blizzard (22), are summarized in Table 2, whereas the main features of APS-2, as defined according to the more recent nosological classification (1, 2), are given in Table 1.

### *Peculiarities of IPEX*

This monogenic syndrome of X-linked polyendocrinopathy, immune dysfunction and enteropathy is very rare, may present very early and may be often fatal (1, 2). It results from mutations in the forkhead box protein P3 gene, that controls the normal function of regulatory T cells.

Clinically this syndrome presents during the first few months of life with chronic diarrhea and malabsorption, dermatitis, failure to thrive, T1DM and other autoimmune disorders (Table 1). Due to the severe malnutrition degree and the recurrent infections which result from immunosuppressive therapies, children with this condition usually die during the first two years of life (1, 2). Supportive care and management of underlying clinical problems are mandatory and restoration of normal T-cell function may improve the overall clinical picture. The immunosuppressive medications that have been tried in the management of this syndrome are: ciclosporin, methotrexate, high-dose glucocorticoids, tacrolimus, infliximab and rituximab (27-31). It is very important to suspect and recognize this condition as soon as possible, since an early bone marrow transplantation, with the development of mixed chimerism in the recipient, could stop the natural evolution of this very severe disorder (2). The main peculiarities of this condition in pediatric age are summarized in Table 1.

### **Conclusions**

1) Among the different APSs, the one that is most typical of pediatric age is APS-1; 2) APS-1 is not characterized only by the classical triad (chronic

moniliasis-hyposurrealism-hypoparathyroidism) and its clinical spectrum is enlarging over time; 3) APS-2 may have a different epidemiological and clinical expression according to two different nosological classifications.

### **References**

1. Michels AW, Gottlieb PA. Autoimmune polyglandular syndromes. *Nat Rev Endocrinol* 2010; 6(5): 270-7.
2. Eisenbarth GS. Autoimmune polyendocrine syndromes. *Adv Exp Med Biol* 2004; 552: 204-18.
3. Robles DT, Fain PR, Gottlieb PA, Eisenbarth GS. The genetics of autoimmune polyendocrine syndrome type II. *Endocrinol Metab Clin North Am* 2002; 31(2): 353-68, vi-vii.
4. Betterle C, Volpato M, Greggio AN, Presotto F. Type 2 polyglandular autoimmune disease (Schmidt's syndrome) *J Pediatr Endocrinol Metab* 1996; 9(1): 113-23.
5. Majeroni BA, Patel P. Autoimmune polyglandular syndrome, type II. *Am Fam Physician* 2007; 75(5): 667-70.
6. Perheentupa J. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *J Clin Endocrinol Metab* 2006; 91(8): 2843-50.
7. Cervato S, Mariniello B, Lazzarotto F, et al. Evaluation of the autoimmune regulator (AIRE) gene mutations in a cohort of Italian patients with autoimmune-polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED) and in their relatives. *Clin Endocrinol (Oxf)* 2009; 70(3): 421-8.
8. Cervato S, Morlin L, Albergoni MP, et al. AIRE gene mutations and autoantibodies to interferon omega in patients with chronic hypoparathyroidism without APECED. *Clin Endocrinol (Oxf)* 2010; 73(5): 630-6.
9. Meloni A, Willcox N, Meager A, et al. Autoimmune polyendocrine syndrome type 1: an extensive longitudinal study in Sardinian patients. *J Clin Endocrinol Metab* 2012; 97(4): 1114-24.
10. Valenzise M, Wasniewska M, Mirabelli S, De Luca F, Cervato S, Betterle C. Identification of two novel mutations in the first Sicilian APECED patient with no R203X mutation in AIRE gene and review of Italian APECED genotypes. *Gene* 2012; 499(2): 343-6.
11. Valenzise M, Fierabracci A, Cappa M, et al. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy: report of seven additional sicilian patients and overview of the overall series from sicily. *Horm Res Paediatr* 2014; 82(2): 127-32.
12. Meloni A, Perniola R, Faà V, Corvaglia E, Cao A, Rosatelli MC. Delineation of the molecular defects in the AIRE gene in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy patients from Southern Italy. *J Clin Endocrinol Metab* 2002; 87(2): 841-6.
13. Zlotogora J, Shapiro MS. Polyglandular autoimmune syndrome type I among Iranian Jews. *J Med Genet* 1992; 29(11): 824-6.

14. Perri V, Giancchetti E, Scarpa R, et al. Altered B cell homeostasis and Toll-like receptor 9-driven response in patients affected by autoimmune polyglandular syndrome Type 1: Altered B cell phenotype and dysregulation of the B cell function in APECED patients. *Immunobiology* 2016 Sep 9. pii: S0171-2985(16)30363-1. doi: 10.1016/j.imbio.2016.09.001
15. Valenzise M, Alessi L, Bruno E, et al. APECED syndrome in childhood: clinical spectrum is enlarging. *Minerva Pediatr* 2016; 68(3): 226-9.
16. De Luca F, Valenzise M, Alaggio R, et al. Sicilian family with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and lethal lung disease in one of the affected brothers. *Eur J Pediatr* 2008; 167(11): 1283-8.
17. B Shum AK, Alimohammadi M, Tan CL, et al. PIFB1 is a lung-specific autoantigen associated with interstitial lung disease. *Sci Transl Med* 2013; 5(206): 206ra139.
18. Valenzise M, Meloni A, Betterle C, et al. Chronic inflammatory demyelinating polyneuropathy as a possible novel component of autoimmune poly-endocrine-candidiasis-ectodermal dystrophy. *Eur J Pediatr* 2009; 168(2): 237-40.
19. Scarpa R, Alaggio R, Norberto L, et al. Tryptophan hydroxylase autoantibodies as markers of a distinct autoimmune gastrointestinal component of autoimmune polyendocrine syndrome type 1. *J Clin Endocrinol Metab* 2013; 98(2): 704-12.
20. Alimohammadi M, Dubois N, Sköldbberg F, et al. Pulmonary autoimmunity as a feature of autoimmune polyendocrine syndrome type 1 and identification of KCNRG as a bronchial autoantigen. *Proc Natl Acad Sci USA* 2009; 106(11): 4396-401.
21. Su MA, Davini D, Cheng P, et al. Defective autoimmune regulator-dependent central tolerance to myelin protein zero is linked to autoimmune peripheral neuropathy. *J Immunol* 2012; 188(10): 4906-12.
22. Neufeld M, Maclaren N, Blizzard R. Autoimmune polyglandular syndromes. *Pediatr Ann* 1980; 9(4): 154-62.
23. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. *Endocr Rev* 2002; 23(3): 327-64.
24. Schatz DA, Winter WE. Autoimmune polyglandular syndrome. II: Clinical syndrome and treatment. *Endocrinol Metab Clin North Am* 2002; 31(2): 339-52.
25. Kahaly GJ. Polyglandular autoimmune syndromes. *Eur J Endocrinol* 2009; 161(1): 11-20.
26. Schneller C, Finkel L, Wise M, Hageman JR, Littlejohn E. Autoimmune polyendocrine syndrome: a case-based review. *Pediatr Ann* 2013; 42(5): 203-8.
27. Levy-Lahad E, Wildin RS. Neonatal diabetes mellitus, enteropathy, thrombocytopenia, and endocrinopathy: Further evidence for an X-linked lethal syndrome. *J Pediatr* 2001; 138(4): 577-80.
28. Wildin RS, Smyk-Pearson S, Filipovich AH. Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. *J Med Genet* 2002; 39(8): 537-45.
29. Bindl L, Torgerson T, Perroni L, et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). *J Pediatr* 2005; 147(2): 256-9.
30. Battaglia M, Stabilini A, Migliavacca B, Horejs-Hoeck J, Kaupper T, Roncarolo MG. Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. *J Immunol* 2006; 177(12): 8338-47.
31. Coenen JJ, Koenen HJ, van Rijssen E, et al. Rapamycin, not cyclosporine, permits thymic generation and peripheral preservation of CD4+ CD25+ FoxP3+ T cells. *Bone Marrow Transplant* 2007; 39(9): 537-45.

Received: 3 November 2016

Accepted: 11 December 2016

Correspondence:

Dott.ssa Giuseppina Salzano,

Dipartimento di Patologia Umana dell'Adulto

e dell'età evolutiva, Policlinico Universitario di Messina,

Via Consolare Valeria, 98125 Messina, Italy

Tel. +39 090 2213157

Fax +39 0902212143

E-mail: gsalzano@unime.it