TYPES OF POLYGLANDULAR AUTOIMMUNE SYNDROMES AT ADULTS PATIENTS WITH DIABETES MELLITUS AND THYROID DISEASES

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Abstract
Background/Objectives: Polyglandular autoimmune syndrome (PAS) is made up of a group of autoimmune disorders of the endocrine glands. The purpose of this study is to determine the types of PAS in a group of adults with thyroid diseases and diabetes mellitus (DM).
Material and methods: The studied group was of 350 cases with an age between 17-79 years. The methods of investigation were represented by clinical, imaging, biochemical, hormonal and immunological parameters.
Results: The prevalence of PAS in the study group was 17.14%, from which PAS I 0%, PAS II 3.14% (11.66% in the case of DM type 1 and 1.38% in the case of DM type 2, $p < 0.001$, $X^2 = 17.28$) and PAS III 14% (71.66% in the case of DM type 1 vs. 2.06% in the case of DM type 2, $p < 0.001$, $X^2 = 200.01$). The type of PAS III was type III A for type 1 diabetes and type III C for type 2 diabetes. All the patients with PAS were middle-aged women.
Conclusions: In our study group we find PAS at middle-aged women, the type II and III, which are prevailed in the group with type 1 diabetes, due to autoimmune origin.

Keywords: Diabetes mellitus, thyroid disease, polyglandular autoimmune syndromes, adults

Introduction

The present study regards a topic of general interest, because it knows a few about the types and prevalence of polyglandular autoimmune syndrome (PAS) at adult's patients with diabetes mellitus (DM).

PAS is made up of a group of autoimmune disorders of the endocrine glands [Kahaly, 2009] and comprise endocrine, neurological, dermatological, gastroenterological and other diseases, which are in common autoimmune pathogenesis. Endocrine pathology may manifest as hypo-or hyper function of interested gland [Şerban, 2010].

PAS syndromes include: PAS I, PAS II, PAS III, IPEX (XPID) syndrome (X-Link poliendocrinopathies, immune dysfunction, and diarrhea), non-organ-specific autoimmunity (such as systemic lupus erythematosus) + insulin anti-receptor antibodies, thymic tumors + autoimmune endocrinopathies, Graves disease + Hirata syndrome (anti-insulin autoantibodies), POEMS syndrome (polyneuropathy + organomegaly + endocrinopathy + monoclonal serum protein + skin changes), congenital rubella, followed by the appearance of thyroiditis and type 1 diabetes ± other autoimmune diseases. Of these, the most common are PAS I, II and III [Şerban, 2010].

PAS type I (PAS I) is an autosomal recessive disorder caused by a mutation in the short arm of chromosome 21, characterized by the triad: muco-cutaneous candidiasis, hypoparathyroidism and Addison's disease. The symptoms and signs appear in childhood; candidiasis is usually the first sign, followed usually by hypoparathyroidism and Addison disease [Aldasouqi et al, 2006, Myhre et al, 2001]. DM type 1 occurs in less than 4% of affected children, but increases to 12% by adults. Its incidence is <1/100000/year, being higher in communities where there is a high degree of consanguinity and F/M ratio is 0.8 - 2.4:1 [Sivarajah et al, 2006].

PAS type II (PAS II) is the most common endocrinopathy and is characterized by: Addison's disease, Grave's disease, autoimmune chronic thyroiditis (ACT)**,** diabetes mellitus (DM) type 1, primary hypogonadism**,** myasthenia gravis and celiac disease. Most disorders are associated with the following HLA: A1, B8, DR3 (DQA1 * 0501, DQB1 * 0201) and DR4 (DQA1 * 0301, DQB1 * 0302) [Sivarajah et al, 2006, Betterle et al, 2004].

The most frequent clinical combination association is Addison disease and Hashimoto thyroiditis, while the least is Addison disease, Graves's disease, and DM type 1 (Carpenter syndrome).

PAS II occurs in adulthood, usually around the third and fourth decades of life. In United States, its frequency is 14-20 people per million and the female-to-male ratio is 3-4:1 [Obermayer-Straub et al, 1998].

PAS type III (PAS III) is a **PAS II** syndrome, but without the adrenocortical involvement[8]. This syndrome is associated with diseases as: organ-specific autoimmune diseases (celiac disease, hypogonadism, and myasthenia gravis), organ-nonspecific or systemic autoimmune diseases (sarcoidosis, Sjogren syndrome, and rheumatoid arthritis), other diseases (gastric carcinoid tumor, malabsorption due to exocrine pancreatic deficiency), and may be classified into 3 subcategories:

- PAS III A – ACT with immune-mediated DM
- PAS III B - ACT with pernicious anemia
- PAS III C - ACT with vitiligo and/or alopecia and/or other organ-specific autoimmune disease

The exact international prevalence of PAS III is unknown. PAS III appears in middle-aged women but can occur in persons of any age; prevailed in females and no racial or ethnic differences in its frequency have reported [Aung et al, 2006].

Autoimmune disease affecting a single endocrine gland is frequently followed by impairment of other glands, resulting in multiple endocrine failures. The identification of circulating organ-specific auto antibodies provided the earliest and strongest evidence for the autoimmune pathogenesis of polyglandular failure syndromes [Aung et al, 2006].

The diagnosis is established based on the symptoms and clinical manifestations of each case and it is recommended metabolic, hormonal and immunological investigations to confirm it [Șerban, 2010].

Treatment consists of hormone replacement for endocrine deficiencies, and it is specific for each disease in part. If it is instituted early, the patients have a good evolution and don't develop complications [Șerban, 2010].

The patients with PAS and their relatives should be monitored for life, because it is the risk for appearance for a new endocrinopathies. Monitoring is the periodic physical examination and specific tests, and counseling patients and their relatives, regarding early signs and symptoms of major components of the syndrome [Șerban, 2010].

The aims of the present study were to evaluate the prevalence of different types of PAS at adult's patients with DM and thyroid diseases.

Material and method

Material

Investigated population

350 people with DM (307 F and 43 M), aged between 18 and 79 years represented the studied group. Depending on glycemic balance, the group was divided into:

- the group with DM type 1 – 60 (17.14%) (55 F and 5 M)
- the group with DM type 2 – 290 (82.86%) (252 F and 38 M) (Fig.1)

The subjects were investigated in the Clinic of Endocrinology, Timisoara, Romania, in the period January 2001 to December 2005.

The study inclusion criteria were age over 18 years and the presence of DM and of thyroid disease.

The study was approved by the local ethics committee. All patients provided oral informed consent.

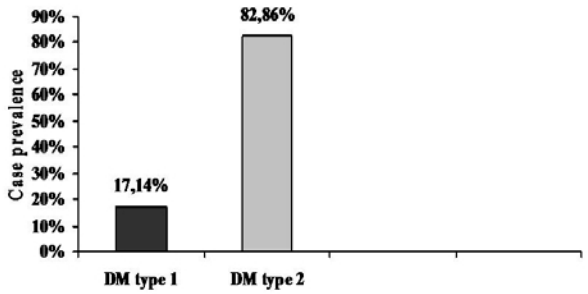

Fig. 1. Cases classification depending on glycemic balance

Methods of investigation

The methods of investigation were represented by **clinical data** - case history, current status, **imagistic**- thyroid ultrasound, **biochemical** - for ***glycemic balance***: fasting blood glucose, glycosylated hemoglobin, ***investigation of the thyroid gland***: TSH, FT_4, FT_3, thyroid antibodies, ***investigation of the adrenal gland***: cortisol, ACTH, 21-hydroxylase antibodies, ***gonadotropins***: FSH, LH and appropriate sex hormones (testosterone, estradiol), ***investigation of celiac disease***: ant tissue transglutaminase antibodies, ***investigation of pernicious anemia***: complete blood count with mean cell volume and vitamin B_{12} levels, parietal cell and anti-intrinsic factor antibodies.

Determination of plasma glucose was performed by enzyme technique with glucosooxidasis. Normal values: 70 - 110 mg%; DM - values equal or over 126 mg%.

Determination of HbA1c was achieved through the DiaStat for measuring HbA1c reported to the total HbA.

The TSH level in plasma, the free fraction of triiodotironin (FT_3), and the plasma free fraction of thyroxin (FT_4) were performed with ARCHITECT quantitative method, which is an immunological method, Chemilumnescent Microparticle Immunoassay (CMIA). Normal values: TSH = 0.465-4.68 Miu/ml, FT_3 = 3.69 -10.4 pmol/l, FT_4 = 10-28.2 pmol/l.

The level of cortisol was performed by IMMULITE / IMMULITE 1000 technique, an imunometric method, of chemiluminescent, Immuno Chemilumino Enzymometric assay (ICEM). Normal value: a.m. 5-25 microgram/dl.

FSH level was measured quantitatively by the ARCHITECT method; a CMIA. Reference values are shown in Table 1.

Table 1. The reference values for FSH

Population field	mIU/ml
Women:	
- Follicular phase	3.35 – 21.63
- Ovulating phase	4.97 – 20.82
- Luteal phase	1.11 – 13.99
- Postmenopausal	2.58 – 150.53
Men	1.37 – 13.58

Testosterone was determinate by ELISA method. References values: Adults: men: 0.019-0.145 nmol/L; women in fertile period: <0.014 nmol/L; pills: 0.001-0.0069 nmol/L; postmenopausal: 0.0003-0.0058 nmol/L.

Estradiol was determinate by immunochemical with electrochemiluminiscent detection method (ECLIA). References values are shown in Table 2.

Table 2. The reference values for estradiol

Population field	pg/ml
Women:	
- Follicular phase	35 -169
- Ovulating phase	49 - 427
- Luteal phase	53 -191
- Postmenopausal	18 -110
Men	25 -107

To determine ***serum levels of antiperoxidase (antiTP) and antithyroglobulin (antiTg) antibodies*** it was used the kit AxSYM antiTPO, respectively the kit AxSYM antiTg, and an immunological method (Microparticle Enzyme Immunoassay) (MEIA). Normal values: antiTPO antibodies <35 IU/ml, antiTg antibodies <55 IU/ml.

To determine ***21-hydroxylase (anti 21-OH antibodies) antibodies level*** it was used the radioimunodetermination method combined with a technique of imunoprecipitation. Normal range: <1 IU/ml

ACTH was determinate by immunoassay with chemiluminescent detection method.

Antitissue transglutaminase antibodies were determinate by ELISA method. References values: IgA, IgG : <10 U/mL: negative; ≥10 U/mL: positive.

Vitamin B_{12} levels were determinate by immunochemical with ECLIA method. References values: 191-663 pmol/L (for european population).

Parietal cell antibodies were determinate by indirect immunofluorescence. References values: negative.

Anti-intrinsic factor antibodies were determinate by ELISA method. References values: < 6 U/mL: negative.

Determination of complete blood count was achieved with electric impedance method. Normal values: erythrocytes = 4-5.5 mil/mm^3 (men: 4.9 ± 0.7 mil/mm^3, women: 4.3 ± 0.6 mil/mm^3), leucocytes = 5000 – 9000 mil/mm^3, plateled = 150000 – 350 000/mm^3, hematocrit: men 45 ± 7%, women 42 ± 5%, hemoglobin: men: 15 ± 2 g/dl, women: 14 ± 2 g/dl.

Constants and red cell indices are calculated automatically, depending on the values of hemoglobin, hematocrit and red blood cell count. Normal values**:** mean corpuscular volume = 80-100 fl, mean corpuscular hemoglobin concentration = 32-36 g Hb/100 ml erythrocytes, mean corpuscular hemoglobin = 27-32 pg.

Thyroid ultrasound was performed in all cases and allowed us to measure thyroid volume, thyroid study and the changes in parenchyma's density.

Normal thyroid parenchyma presents an increased density, uniform, while inflammatory processes and autoimmune pathology appears hypo dens.

ACT disorder appears with a hypoecogenity of the parenchyma and normal or increased thyroid volume.

Statistical analysis

For statistical analysis we used Microsoft Excel and POP Tools from Microsoft Office 2003 and EPI 2000 program. To measure the quantitative variables were determined media and standard deviation, and to assess the gender differences and other differences we used the unpaired t test and ANOVA test, considering statistically significant a $p < 0.05$.

Results and discussion

In the group of adults 17.14% had DM type 1 and 82.86% had DM type 2**.**

The prevalence of PAS was 17.14%, from which PAS I 0%, PAS II 3.14% and PAS III 14% (Table 3).

Table 3. Prevalence of PAS in the study group

Types of PAS	**Subject group**	
	No.	**%**
PAS I	0	0 %
PAS II	11	3.14 %
PAS III	49	14%

We don't find **PAS I** in our study group.

The prevalence of **PAS II** was 3.14 % (11.66% for DM type 1 and 1.38% for DM type 2, $p = 0.00003$, $X^2 = 17.28$) (Table 4).

Table 4. The prevalence and characteristic of PAS II in the study group

Associations	DM type 1 DM type 1 + ACT + asimtomatic Addison disease	DM type 2 DM type 2 + ACT + Addison disease
Prevalence	11.66%	1.38%
Gender	female	female
Family history of thyroid disease	none	none
Actual age (years)	44.28±23.57	61.75±7.32
Onset age of thyroid disease (years)	37.33 ± 2.42	60.75±8.38
Onset age of DM (years)	14.83 ± 10.88	59.75 ± 7.22
DM duration (years)	24.83 ± 8.75	2 ± 0.81
Thyroid disease duration (years)	2.33 ± 0.51	1 ± 1.41
BMI (kg/m^2)	25.72 ± 2.65	32.75 ± 4.42
Glycemia (mg%)	268.83 ± 139.73	94.75 ± 36.79
HbA_{1c} (%)	12.93 ± 5.4	6.22 ± 2.11
DM	clinically manifest	asymtomatic
DM treatment	insulin in different therapeutic schemes	diet

In 2 cases, the first disease was DM type 1; follow by ACT after 2±0.5 years. In 5 cases, the first disease was ACT; follow by DM type 1 after 27.8 ± 23.13 years.

For appreciation association of Addison disease, were determinate plasma cortisol and 21-OH antibodies. The 21-OH values were significally higher in 7 cases, all theses were clinically asymptomatic.

In the case of DM type 2 all the 4 cases with Addison diseases were symptomatic; the diagnosis was early, base on clinical symptoms. In the case of association between Addison disease and ACT, the first imunophathy was Addison disease; follow after 16 years by ACT.

The prevalence of **PAS III** was 14% (100% F and 0% M, $p<0.001$, $X^2 = 52.69$).

PAS III prevalence in DM type 1 was 71.66% (100% F and 0% M, $p<0.001$, $X^2 = 67.01$) and 2.06% in DM type 2 (100% F and 0 % M, $p = 0.01$, $X^2 = 6.06$) (71.66% vs. 2.06%, $p <0.001$, $X^2 = 200.01$).

In the case of DM type 1 we have PAS III A, and in the case of DM type 2 only PAS III C. (Fig. 2).

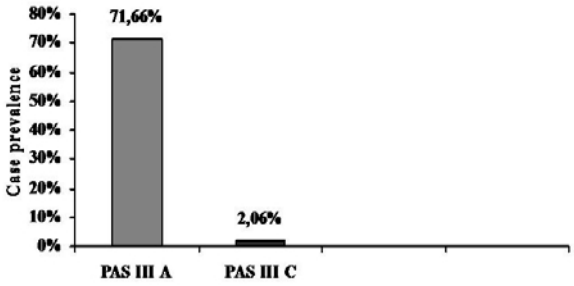

Fig. 2. Types of PAS III in the study group

In the group with ***DM type 1*** the main endocrine immune combinations were represented by DM type 1 with ACT. Other endocrine immune associations were represented by autoimmune ovarian insufficiency (AOI) and the no endocrine disorders as vitiligo, alopecia, and Biermer anemia (Table 5).

Table 5. Prevalence of PAS III in the study group

Associations	**Subject group**	
	No.	**%**
DM type 1	60	
DM type 1 + ACT	31	51.66%
DM type 1 + ACT + decalvant pelada	2	3.33%
DM type 1 + ACT + vitiligo	3	5%
DM type 1 + ACT + autoimmune ovarian failure	6	10%
DM type 1 + ACT + vitiligo + Biermer anemia	1	1.66%
DM type 2	290	
DM type 2 + ACT + vitiligo	6	2.06%

In the group of adults with DM type 1 the first imunopathy was DM type 1, present in 24 of cases and was associated with ACT in all 24 cases. In 2 cases, thyroid disorder and DM type 1 were detected at the same time. In 17 cases thyroid disorder preceded the DM type 1.

For detect AOI was determine the levels of FSH, increased > 25 IU/l in 6 cases. Primary ovarian insufficiency (early menopause) usually occurs before the age of 40 years (in the absence of iatrogenic causes) and its clinical signs are secondary amenorrhea and hypergonadotropism with hypoestrogenemia.

AOI is usually associated with other autoimmune pathology such as DM type 1, Addison's disease, ACT, vitiligo, etc.; its diagnosis is difficult

and it is usually based on the exclusion of other possible causes of primary ovarian insufficiency and the notice of autoimmune etiology [Aung et al, 2006].

Also estrogen therapy in AOI may increase the risk of cardiovascular disease [Kalantaridou et al, 1999].

In 4 cases was associated vitiligo and in 2 cases decalvant pelada, which occurred before the onset of endocrine immunopathys. In one case was associated more than one nonendocrine autoimmune disorder respectively Biermer anemia and vitiligo.

In adults, the average time between the onset of type 1 DM and ACT was 22.29 ± 12.42 years.

In 17 cases the first immunopathy was ACT, followed by DM type 1 after 2.47 ± 1.94 years.

The characteristic and prevalence of PAS III in DM type 1 and 2 group are show in Table 6.

Table 6. The characteristic of PAS III in the study group

	DM type 1	**DM type 2**
Prevalence	71.66%	2.06%
Gender	female	female
Family history of thyroid disease	none	none
Actual age (years)	43 ± 18.95	55 ± 14.14
Onset age of thyroid disease (years)	30.46 ± 22.94	53.5 ± 12.02
Onset age of DM (years)	31.84 ± 25.21	57 ± 4.94
DM duration (years)	16.25 ± 13.71	0
Thyroid disease duration (years)	4.56 ± 4.17	25.6 ± 24.15
BMI (kg/m^2)	25.19 ± 3.51	28.24 ± 7.66
Glycemia (mg%)	196.81 ± 89.19	99 ± 18 mg%
HbA_{1c} (%)	10.94 ± 3.85	5.06 ± 0.69
DM	clinically manifest	asymtomatic
DM treatment	insulin in different therapeutic schemes	diet

Prevalence of ACT in ***DM type 2*** was 26.55% (77 patients, 69 F and 8 M). In adults with DM type 2 PAS type III was found in 6 (2.06%) cases, of which all have ACT + vitiligo. The first disease was vitiligo follow by ACT after 2-5 years. DM type 2 appears after ACT, at 5-10 years, possible because of replacement therapy for thyroid disease.

Also in these cases it is useful to determinate the antibodies for diabetes because these patients may have latent autoimmune diabetes (LADA) and in time requires insulin.

In general, in the first stage of PAS, antibodies levels are elevated. In the second stage the disease is sub clinical and in the third stage becomes clinically manifested.

By ACT, 24 cases were euthyroid and 96 cases hypothyroid (76 clinical cases and 20 cases sub clinical). 24 cases did not require treatment; the remaining had substitution treatment with thyroid hormones. AntiTPO antibodies were present in 27 cases of ACT and DM type 1, the remaining cases presenting insignificant values.

Discussion

PAS I comprises candidiasis, hypoparathyroidism, and adrenal failure [Alimohammadi et al, 2008] (a case without mucocutaneous candidiasis has been reported in an adolescent [Bhansali et al, 2003]).

In North America studies about PAS I was published by Neufeld and colleagues in 1981 and by Heino and coauthors in 1999 [Neufeld et al, 1981, Heino et al, 1999]. In the latter report, 16 patients were described, including 13 white patients, 1 Hispanic individual, 1 Middle Eastern patient, and 1 Asian person.

In Europe, PAS I cluster in certain homogeneous ethnic populations due to consanguineous marriages. It is more common in Finland (1 case per 25,000 [Bjorses et al, 2000]), in Sardinians (1 case per 14,400) and in Iranian Jews (1 case per 9,000) [Rosatelli et al, 1998, Zlotogora et al, 1992] and is less frequent in northern Italy, northern Britain, Norway, and Germany.

It usually occurs in children aged 3-5 years or in early adolescence (always in the early part of the third decade of life); F/M ratio is 0.8 - 2.4:1 [Dittmar et al, 2003]. The genetic mode of transmission is autosomal recessive, although an X-linked inheritance fashion in a female was report from Italy, by Iannello and colleagues [Iannello et al, 1997].

Because PAS I is very rare and occurs in children, we don't find this syndrome in our study (one of the criteria was the age over 18 years).

PAS II is characterized by the obligatory occurrence of autoimmune Addison disease in combination with ACT and/or type 1 diabetes, but can comprise also primary hypogonadism, myasthenia gravis, and celiac disease. The prevalence of PAS II is 1:20 000 [Cooper e al, 2003] and appears usually in women (F/M = 1:3) [Fo¨rster et al, 1999]. It occurs at ages 20–60 years, mostly in the third or fourth decade [Ten et al, 2000], and it is common for multiple generations to be affected by one or more component of the disease [Neufeld et al, 1980]. While there is some correlation between the ages of onset of one PAS illness with another, many years may separate the onset of different diseases [Fo¨rster et al, 1999]. All the disorders resulting in tissue destruction appear to have a prolonged phase of cellular loss preceding overt autoimmune glandular disease [Kahaly, 2009].

In a study perform by Betterle et al, DM was found in 57–63% of cases, while Addison's disease preceded DM in 23–35% and the two diseases appeared to be simultaneous in 8–10% of cases; in 4% of patients the sequence of the diseases was not specified. Many patients with this association died within one year by the time of the clinical diagnosis [Betterle et al, 2004].

In our study, the prevalence of **PAS II** in the study group was 3.14 % (11.66% for DM type 1 and 1.38% for DM type 2, $p = 0.00003$, $X^2 = 17.28$). All patients were middle – aged women, so concordant with literature data.

The low frequency of PAS II in our study can be due by the low number of patients with DM type 1 and thyroid disease and because many patients with Addison disease died at a short time after diagnosis, before to be investigate for DM type 1.

In the case **of PAS III**, the exact international prevalence and in the United States is unknown. No racial or ethnic difference in frequency of PAS III has been reported. It is more common in females than in males and typically is observed in middle-aged women but can occur in persons of any age.

The prevalence of **PAS III** in the study group was 14% (71.66% for DM type 1 and 2.06% for DM type 2, $p < 0.001$, $X^2 = 200.01$). All patients were middle-aged women, so concordant with literature data.

Hunger –Batterfeld et al studied the prevalence of PAS in 139 patients with DM type 1 and found in 24.5% ACT, in 4.3% Graves' disease, in 1.4% Addison's disease, in 1.4% celiac disease, in 7.2% pernicious anemia, in 0.7% hypophysitis and in 0.7% hypogonadism [Hunger-Battefeld et al, 2009].

In our study, in some cases, one of the disease was asymptomatic, characterized by increased of specific antibodies.

In DM type 1 is ideal to determine the presence of antibodies because they may be present in subjects without clinical symptoms. If their levels are raised, it is good to monitor annual the TSH level and if it is normal it is recommended to doze antithyroid antibodies by intervals of 2-3 years [Eisenbarth et al, 2004, Tunbridge et al, 2000].

Also, if the disease is autoimmune, the patient should be investigated for other autoimmune associations of endocrine or nonendocrine nature.

If DM type 2 is present it is recommended to evaluate TSH levels, and if it is normal, to repeat this evaluation every 5 years.

If pre-existing thyroid pathology is present it is recommended to evaluate plasma glucose levels annually.

Conclusion

In our study group we find PAS at middle-aged women, the type II and III, which are prevailed in the group with DM type 1, due to autoimmune origin.

Regarding PAS type III, we encountered type III A in DM type 1and type III C in DM type 2 (this may be LADA).

Because one of the disease was asymptomatic, characterized by increased of specific antibodies, we must investigate this for another possible autoimmune disease.

Active detection of patients with PAS allows an early diagnosis and an appropriate treatment, to prevent complications, which prolongs the life of patients and improve its quality.

The PAS classification is not final. This may change over time, with the onset of new endocrine disorders or associations with new autoimmune determination.

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