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15-year old girl with PAS type IIIc, 12 months post-thymectomy remission of myasthenia gravis and Graves' disease – case report

15-letnia dziewczynka z PAS typ IIIC, obserwacja 12 miesięcznej remisji miastenii gravis oraz choroby Graves'a po zabiegu tymektomii – opis przypadku

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Abstract
Polyglandular autoimmune syndromes (PAS) is a group of heterogenous conditions characterized by the association of at least two organ-specific autoimmune disorders, concerning both endocrine and non-endocrine organs. Type III is defined as the combination of autoimmune thyroid disease and other autoimmune condition (other than Addison's disease) and is divided into four subtypes. We describe a teenage female patient – with the family history of autoimmune diseases, who has simultaneously developed the symptoms of autoimmune thyroid disease with the clinical picture of hyperthyroidism and myasthenia gravis at the age of fifteen. Graves' disease was diagnosed approximately 2 months before myasthenia. Co-occurance of those two diseases allowed us to diagnose PAS type IIIC, however it caused specific diagnostic and treatment difficulties. Furthermore, several months after the diagnosis the patient was found to be GAD-Ab positive, whilst the glycaemic control remained normal. No evidence of other autoimmune conditions was observed. This patient received the standard GD and MG treatment. When the CT scan revealed thymus enlargement, thymectomy was performed. After the surgery we have observed not only remission of MG, but also a significant decrease of TRAb as well, that lasted for a year after the thymectomy. Our patient's case suggests that in patients diagnosed with PAS, the organ-specific Ab screening can help identify other latent and subclinical autoimmune diseases before clinical symptoms develop. The achievement of post-thymectomy remission of both MG and GD may indicate a close immunological relationship between PAS components.
Key words
autoimmune polyglandular syndromes, Graves' disease, myasthenia, children

Streszczenie
Autoimmunologiczne zespoły wielogruczołowe (PAS) to niejednorodna grupa jednostek klinicznych, które charakteryzuje współwystępowanie co najmniej dwóch specyficznych tkankowo schorzeń o podłożu autoimmunologicznym – dotyczących zarówno narządów wydzielania wewnętrznego, jak i obejmujących narządy pozaendokrynne. Typ III jest warunkowany obecnością przewlekłej choroby zapalnej tarczycy i innej choroby o podłożu autoimmunologicznym (poza chorobą Addisona) oraz podzielony na podtypy. Przedstawiamy nastoletnią pacjentkę z wywiadem rodzinnym obciążonym chorobami autoimmunologicznymi, u której w wieku 15 lat równoczasowo zaobserwowano objawy autoimmunologicznego zapalenia tarczycy o obrazie nadczynności oraz miastenii gravis Rozpoznanie choroby Gravesa-Basedowa wyprzedziło rozpoznanie miastenii o 2 miesiące. Współistnienie tych dwóch schorzeń pozwoliło u pacjentki na stwierdzenie PAS typ IIIC, ale także łączyło się z trudnościami diagnostycznymi i terapeutycznymi. Po kilku miesiącach u pacjentki wykryto także dodatnie miano przeciwciał anty-GAD (przy obserwowanej prawidłowej gospodarce węglowodanowej). Nie stwierdzono dotychczas innych chorób autoimmunologicznych. W przypadku tej pacjentki stosowano typowe leczenie zarówno choroby Gravesa-Basedowa jak i miastenii. Po wykonaniu TK śródpiersia i stwierdzeniu powiększonej grasicy pacjentkę zakwalifikowano do zabiegu tymektomii. Uwagę zwraca nie tylko zmniejszenie dolegliwości związanych z miastenią, ale także znaczący spadek miana przeciwciał TRAb, utrzymujący się przez rok po zabiegu. Powyższy przypadek potwierdza, że u pacjentów z już rozpoznanymi zespołami PAS badanie przeciwciał charakterystycznych dla innych chorób autoimmunologicznych pozwala na wykrycie latentnych postaci choroby zanim jeszcze rozwiną oni objawy, także u pacjentów z już zdiagnozowanym PAS. Osiągnięta po tymektomii remisja obu chorób może wskazywać na istotną współzależność immunologiczną składowych PAS.
Słowa kluczowe
autoimmunologiczne zespoły wielogruczołowe, choroba Gravesa, miastenia, dzieci

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Introduction

A steady rise in autoimmune disease incidence over the last decades is provided in epidemiological data [1]. Among those patients we can observe rare endocrinopathies characterized by the association of at least two organ-specific autoimmune disorders called the polyglandular autoimmune syndromes (PAS).The classification of PAS proposed in 1980 by Neufeld and Blizzard [2] on the basis of clinical features included four main types of PAS and type I, type II, type III, type IV were identified. As regard to PAS type III, it has been subdivided in subgroups, based on the co-existence of a thyroid autoimmune disease (Hashimoto's thyroiditis, Graves' disease GD) with one or more of the autoimmune disorders other than Addison's disease, concerning both endocrine and non-endocrine diseases (e.g. myasthenia gravis, celiac disease, multiple sclerosis, SLE, vitiligo) [3]. (table I) In this article we present a case of patient affected by PAS type IIIC (Graves' disease with concomitant myasthenia gravis).

Case report

Fifteen-year-old female patient, with no previous health problems, good mental and physical development, presented with swallowing difficulties, voice change (especially during longer speeches, decreased physical activity tolerance, increased heart rate, muscle weakness, weight loss with increased appetite, decreased concentration and emotional lability). Initially both the patient and her parents associated those symptoms with stressful situation at school (exams at the end of the school year), but they also observed the intensification throughout the summer vacation. The family medical history consisted mostly of thyroid diseases in her mother (hyperthyroidism) and aunt (hypothyroidism), and Addison's disease in her grandmother. At the Pediatric Neurology Department, where the patient was admitted with the hypothesis of neuromuscular disease, physical examination revealed enlarged thyroid, excessive hand tremor and mild tachycardia (fig. 1). The ulnar nerve electrostimulation was performed (the nerve chosen according to the symptoms and the low traumatization for the patient) – with a negative result excluding myasthenia gravis (MG) from the differential diagnosis at that point (fig. 2A). Further laboratory tests revealed hyperthyroidism with a high concentration of thyroid-specific antibodies (table II). Thyroid ultrasound image showed diffusely enlarged thyroid gland, with increased vascular flow and several small hypoechoic nodules, that confirmed the diagnosis of Graves' disease. The anti-thyroid therapy (methimazole) with propranolol was administered. At the visit in Endocrinological Outpatient Clinic about two months after the diagnosis, the patient presented improvement in some of the previous symptoms, but complained of ptosis, increased swallowing and speaking difficulties, significant voice change. Those symptoms associated with a skin rash (most probable allergic etiology) made parents afraid of possible adverse effects of the treatment, and the girl stopped the medication intake for a few days. The patient was then admitted to the Department of Pediatrics, Endocrinology where the adverse effects of methimazole, as well as other endocrinopathies have been excluded – all the laboratory results remained within normal range. Clinical picture suggested the need of

Table I. Characteristics of PAS type III, modified from Betterle, 2001
Tabela I. *Podział PAS typ III, modyfikacja Betterle, 2001*

Autoimmune thyroid disease			
Hashimoto's thyroiditis Graves' disease Idiopathic myxoedema Symptomless autoimmune thyroiditis Endocrine ophthalmopathy			
+	+	+	+
Type 1 diabetes mellitus Hirata's disease Lymphocytic hyphophysitis POF	Chronic atrophic gastritis Pernicious anemia Celiac disease Chronic Inflammatory bowel diseases Autoimmune hepatitis Primary biliary cirrhosis	Vitiligo Alopecia Myasthenia gravis Stiff-man syndrome Multiple sclerosis	Systemic/Discoid lupus erythematosus Mixed connective tissue disease Rheumatoid arthritis Seronegative arthritis Systemic sclerosis Sjogren's syndrome Werlhof syndrome Antiphospholipid syndrome Vasculitis
3A	3B	3C	3D

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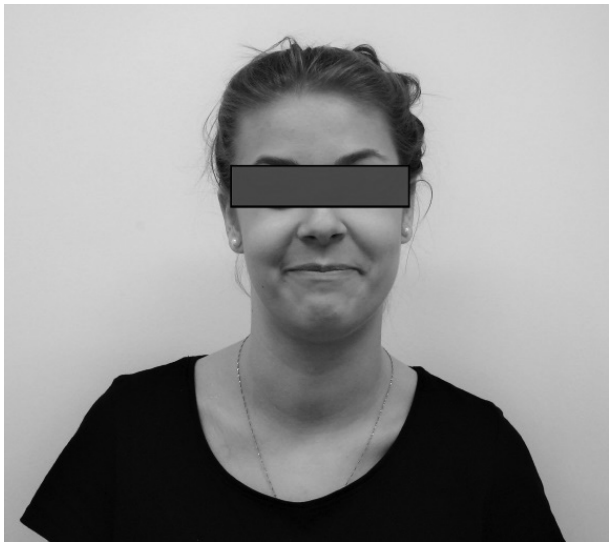

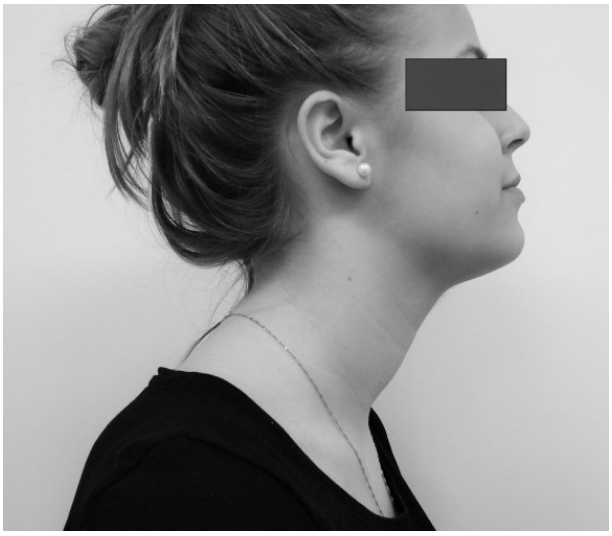

Fig. 1. Physical appearance of the patient, enlarged thyroid
Ryc. 1. *Wygląd pacjentki. Widoczne powiększenie tarczycy*

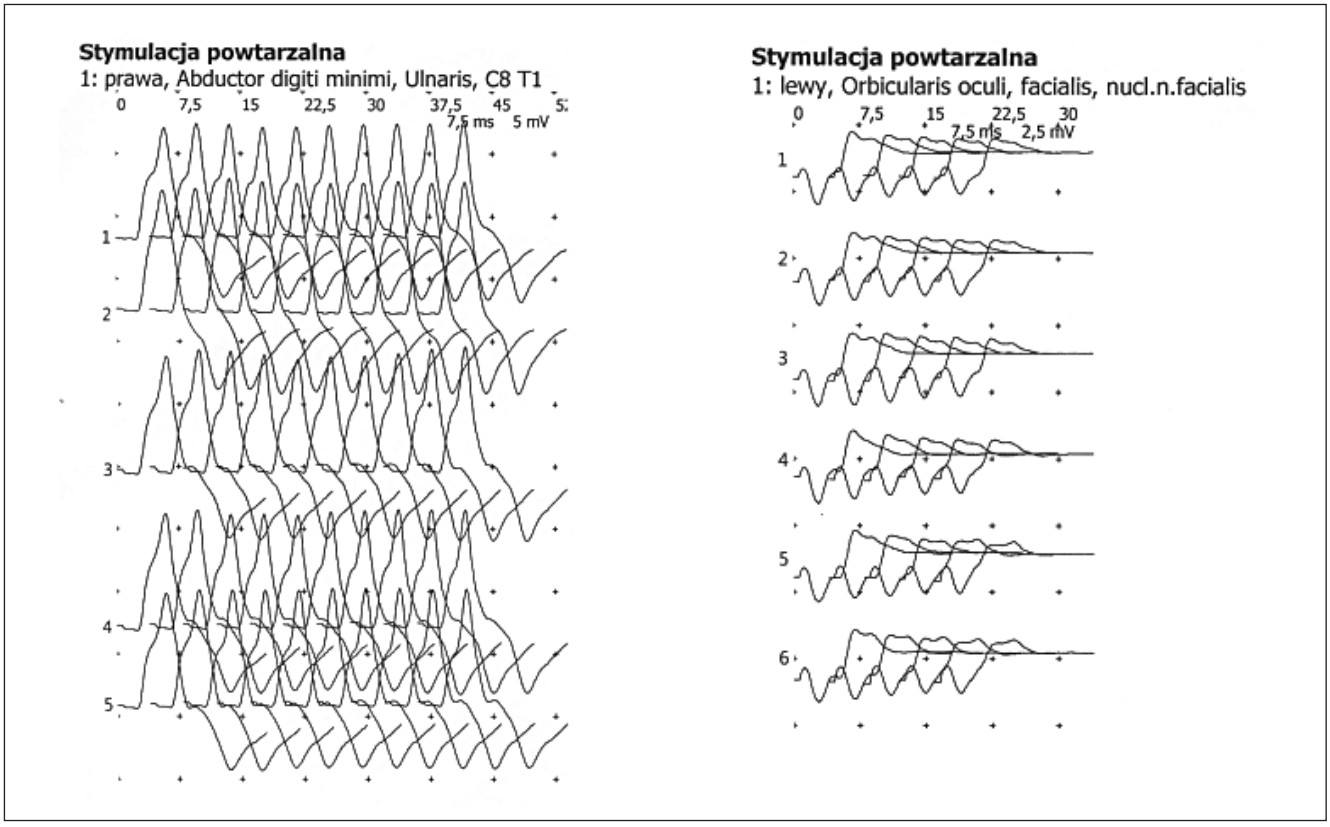

Fig. 2A. Negative result (-) of the ulnar nerve repetitive electrostimulation test
Ryc. 2A. *Ujemny (-) wynik testu elektrostymulacji powtarzalnej nerwu łokciowego*

Fig. 2B. Positive result (+) of facial nerve repetitive electrostimulation test
Ryc. 2B. *Dodatni (+) wynik testu elektrostymulacji powtarzalnej nerwu twarzowego*

Table II. Thyroid function and thyroid-specific antibodies management (AChR-Ab =acetylcholine receptor antibody; ANA Profile = antinuclear antibody profile; TSAb = thyroid stimulating antibody; TBAb = thyroid blocking antibody)
Tabela II. *Funkcjonowanie tarczycy oraz poziom przeciwciał przeciwko tarczycy (AChR-Ab = przeciwciała przeciwko receptorowi acetylocholiny; ANA Profile =profil przeciwciał przeciwjądrowych; TSAb = przeciwciała przeciwtarczycowe stymulujące; TBAb = przeciwciała przeciwtarczycowe blokujące)*

Month of observation	TSH (IU/ml) N: 0,27-4,2	fT4 (ng/ml) N: 1,1-1,8	fT3 (pg/ml) N: 2,3-5,0	ATG (IU/ml)	TPO (IU/ml)	TRAb (IU/L)	Other tests results
Initial visit (11.2014)	<0,005	2,33	6,55	2368	250,5	6,5	
GD treatment (Methimazole + Propranolol) applied							
1 month (12.2014)	0,06	1,74	4,77	2469	212,1	5,83	
2 month (01.2015)	0,02	1,03	3,09	1118	148,8	6,88	AChR-Ab positive
2,5 month (01.2015)	0,12	0,83	2,14			6,20	tTG Ab negative ANA Profile negative
MG treatment (IVIG+Mestinon) added							
3 month (02.2015)	0,08	1,22	3,45			3,67	
4 month (03.2015)	0,03	2,21	5,9			3,03	TSAb – 277 (positive) TBAb – 10 (negative)
5 month (04.2015)	0,01	1.33	4.23			3.88	
6 month (05.2015)	0,43	1,06				4,46	
7 month (06.2015)	1,32	1,32	2,72				
9 month (08.2015)	1,55	1,02	3,32			4,26	
Thymectomy performed (11.2015)							
14 month (01.2016)	0,73	1,13				2,38	
17 month (04.2016)	0,47	1,31				2,6	
20 month (07.2016)	0,35	0,24				2,8	
23 month (10.2016)	0,09					6,72	
25 month (12.2016)	0,01	1,22					

repeating the diagnostic tests for myasthenia gravis – this time the facial nerve electrostimulation test was performed, showing decrease of the muscular response amplitude after a repetitive nerve stimulation with positive result (fig. 2B), laboratory tests revealed the presence of autoantibodies specific to MG (against the acetylcholine receptor) and the chest CT-scan presented thymus enlargement (fig. 3). Co-existance of the autoimmune thyroid disease (GD) and myasthenia gravis in this patient allows us to diagnose PAS type IIIC. In this case the standard MG treatment was administered (intravenous immunoglobulins and pirydostigmine), GD treatment (methimazole) was continued, with fluctuations of thyroid hormone levels observed

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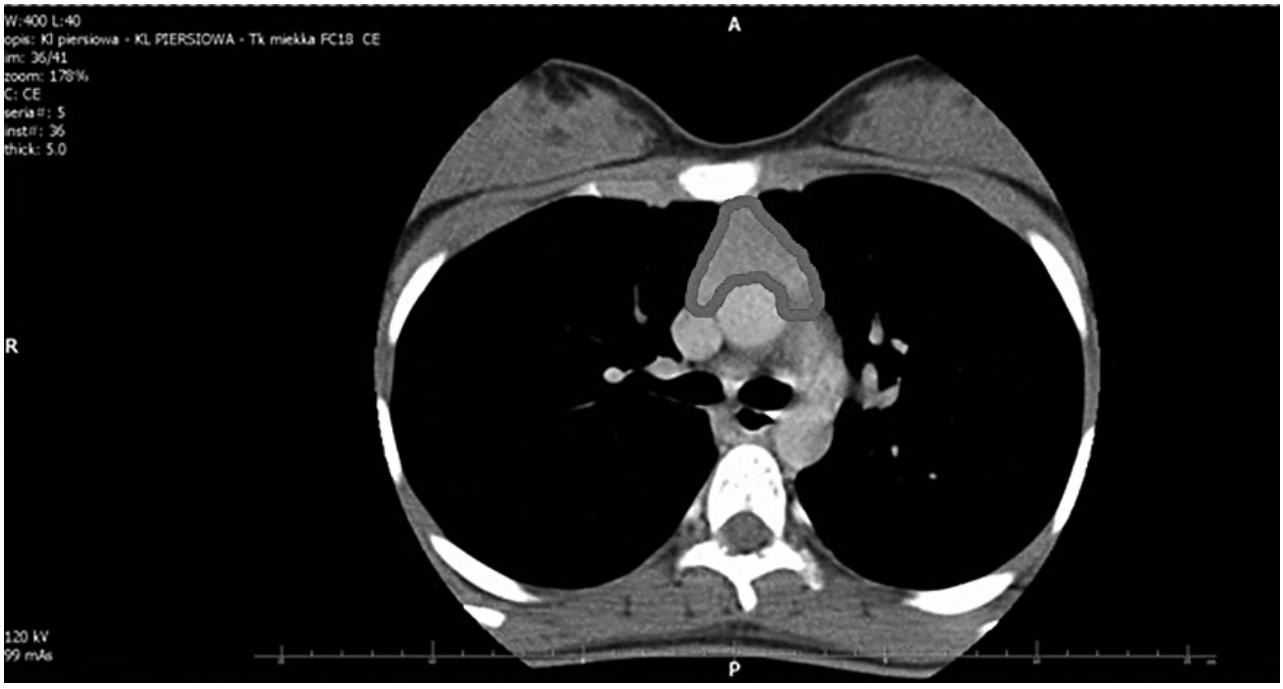

Fig. 3. Chest CT-scan showing abnormal thymus (32 x 40 mm)
Ryc. 3. *TK klatki piersiowej – nieprawidłowa grasica (32x40mm)*

Table III. Organ-specific autoantibodies (tests were carried out by *FIRS Laboratories, RSR Ltd, Parc Ty Glas Llanishen Cardiff,United Kingdom);* GAD65 Ab – ELISA; values of ≥5.0 WHO units/mL) were considered positive. IA-2 Ab – immunoprecipitation assay based on 125I-labelled IA-2 ; values of >1 WHO units/mL were considered positive. Insulin Ab – immunoprecipitation assay ; values of >0.4 U/mL were considered positive ZnT8 Ab – ELISA; values of ≥15 units/mL were considered positive. 21OH Ab – immunofluorescence method with values of >1 U/ml considered positive ARCh Ab – immunoprecipitation assay 125I-labelled; values of ≥ 0.5 nmol/L considered positive

Tabela III. *Przeciwciała narządowo-specyficzne (badania przeprowadzone przez FIRS Laboratories, RSR Ltd, Parc Ty Glas Llanishen Cardiff, United Kingdom) GAD65 Ab – ELISA; wartości ≥5,0 WHO units/mL) uznawano za dodatnieI A-2 Ab – immunoprecypitacja znakowanych 125I IA-2; wartości >1 WHO units/mL uznawano za dodatnieInsulin Ab – immunoprecipitacja; wartości >0,4 U/mL uznawano za dodatnie ZnT8 Ab – ELISA; wartości ≥15 units/mL uznawano za dodatnie 21OH Ab – immunofluorescencja; wartości >1 U/ml uznawano za dodatnie ARCh Ab – immunoprecipitacja, znakowanie 125I; wartości ≥ 0,5 nmol/L uznawano za dodatnie*

	01.2015	11.2015
GAD 65 Ab (U/mL)	(-)	84,5 (+)
IA-2 Ab (U/mL)	(-)	(-)
Insulin Ab (U/mL)	(-)	(-)
ZnT8 Ab (U/mL)	(-)	(-)
21-OH Ab (U/mL)	(-)	(-)
AChR Ab (nmol/L)	7,5 (+)	7,7 (+)

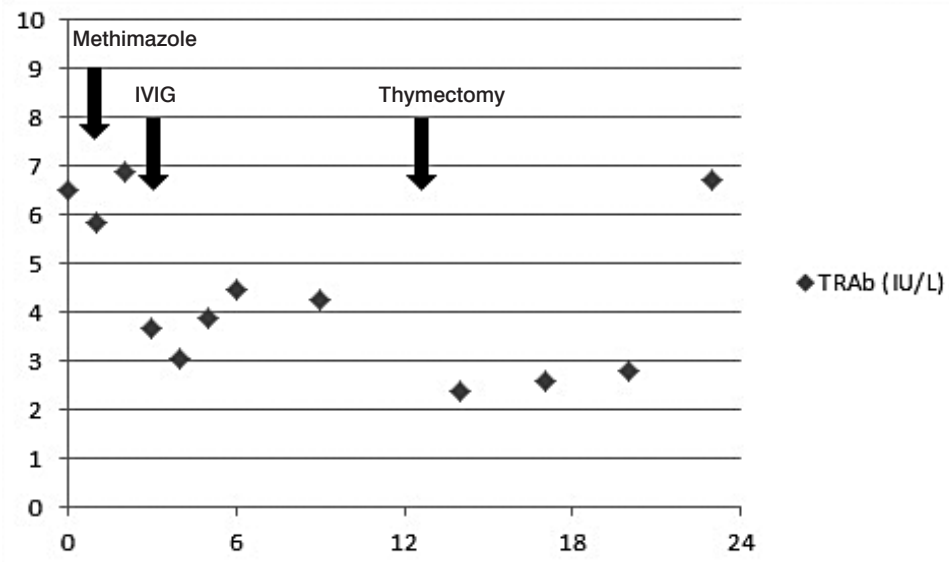

Fig. 4. TSR-Ab fluctuations depending on time (months) and the treatment applied
Ryc. 4. *Wahania TSR-Ab w czasie (miesiące), w odniesieniu do zastosowanego leczenia*

during several months (table II). Interestingly, during the observation the patient presented with GAD-Ab – which were absent at the diagnosis of GD and MG, whilst blood sugar levels remained normal (table III). After about a year after the first diagnosis, thyroid function had stabilized, the patient underwent thymectomy (histopathology revealed the presence of follicular hyperplasia). During one year observation after the surgery not only there was a remission of MG, but a significant decrease of TRAb levels as well (fig. 4). The achieved disease remission and good quality of life lasted for approximately one year, without the necessity for more invasive GD treatment, such as thyroidectomy. However, very recently she presented with a progressive increase of TRAb concentrations and subsequent changes in thyroid hormone levels; in particular suppressed TSH (table II).

Discussion

Coexistence of GD and MG has been described for the first time in 1908 [4] and similar cases have been observed many times in past decades, mostly in adult, female patients [5–8]. In recent years increased incidence has been also observed in younger population [9,10].

In the case of the presented teenage patient, the coexistence of GD and MG, with simultaneously developed symptoms of both diseases caused diagnostic difficulties and important therapeutic implications. The main symptom of MG, which is the muscle weakness [11,12], can be easily confused with thyrotoxicosis symptoms that can involve neuronal paralysis and muscle atrophy [13,14]. Moreover, swallowing problems and voice change, that are common in MG, can be as well caused by enlarged thyroid gland constricting esophagus and pressing laryngeal nerves. Despite the symptoms, that suggested neuromuscular disease, the thyroid abnormality occurred to be more evident in physical examination and laboratory findings at the beginning of diagnostic course, whereas MG diagnostic tests remained negative.

As our patient presented tachycardia and emotional lability in the course of thyrotoxicosis, she was given propranolol in the standard GD management. The previously documented suppressive effect of beta-blockers on the neuro-muscular junction conduction could be the cause of muscle weakness aggravation observed in this patient (increased swallowing problems, more intense voice change, ptosis) [15]. In some described cases, beta-blocker therapy in myasthenia patients caused a range of adverse effects, including breathing difficulties and even a severe respiratory failure [16]. The unstable thyroid hormone levels in our patient had to be concerned in the choice of treatment options for myasthenia gravis and have been the reason for a delay in thymectomy.

Japanese study demonstrated a positive relationship between the clinical activities of GD and MG in 5 patients [17]. Our patient's case and the achieved GD remission with relatively low level of TRAb following the MG treatment (including thymectomy) may reveal another immunological associations with these two components of PAS type IIIC. However, GD relapsed approximatelty one year after thymectomy. Alternatively, the remission of GD may have been related to treatment with anti-thyroid drugs and independent of the effect of thymectomy.

Furthermore, it should be noted that the patient was also positive for GAD-Ab without any impairment of glycaemic control. Other diabetes associated autoantibodies (IA-2 Ab, ZnT8Ab and insulin antibodies) were negative, therefore it is

unlikely that the patient would be at a high risk of progression to type 1 diabetes mellitus [18]. This case highlights the need for diagnostic and immunological vigilance both in the patients with one organ-specific autoimmune disease or with already diagnosed PAS. Detection of specific autoantibody markers for different autoimmune conditions using sensitive and convenient assays would be particularly helpful [3,18]. This strategy may help to identify other latent or subclinical autoimmune disease before clinical symptoms develop. The increased awareness of potential progression to overt autoimmune conditions should lead to better patient care.

Conclusions

A female patient who simultaneously developed autoimmune thyroid disease (GD) and myasthenia gravis was diagnosed with the PAS type IIIC. Post-thymectomy remission of not only MG but also GD was observed for approximately one year. This case provides the new insight to the immunological relationship between PAS components. The co-presence of GAD-Ab highlights the importance of the organ-specific antibody screening for detection of clustering of autoimmune conditions in one patient.

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