

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 miastenu gravis oraz choroby Graves'a po zabiegu tymektomii – opis przypadku

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Abstract

Polyglandular autoimmune syndromes (PAS) is a group of heterogeneous 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-occurrence 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 wielogrzuczołowe (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 pozaendokryne. 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 równocześnie zaobserwowano objawy autoimmunologicznego zapalenia tarczycy o obrazie nadczynności oraz miastenu gravis. Rozpoznanie choroby Gravesa-Basedowa wyprzedziło rozpoznanie miastenu 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 miastenu. 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 one 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 wielogrzuczołowe, choroba Gravesa, miastenia, dzieci



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

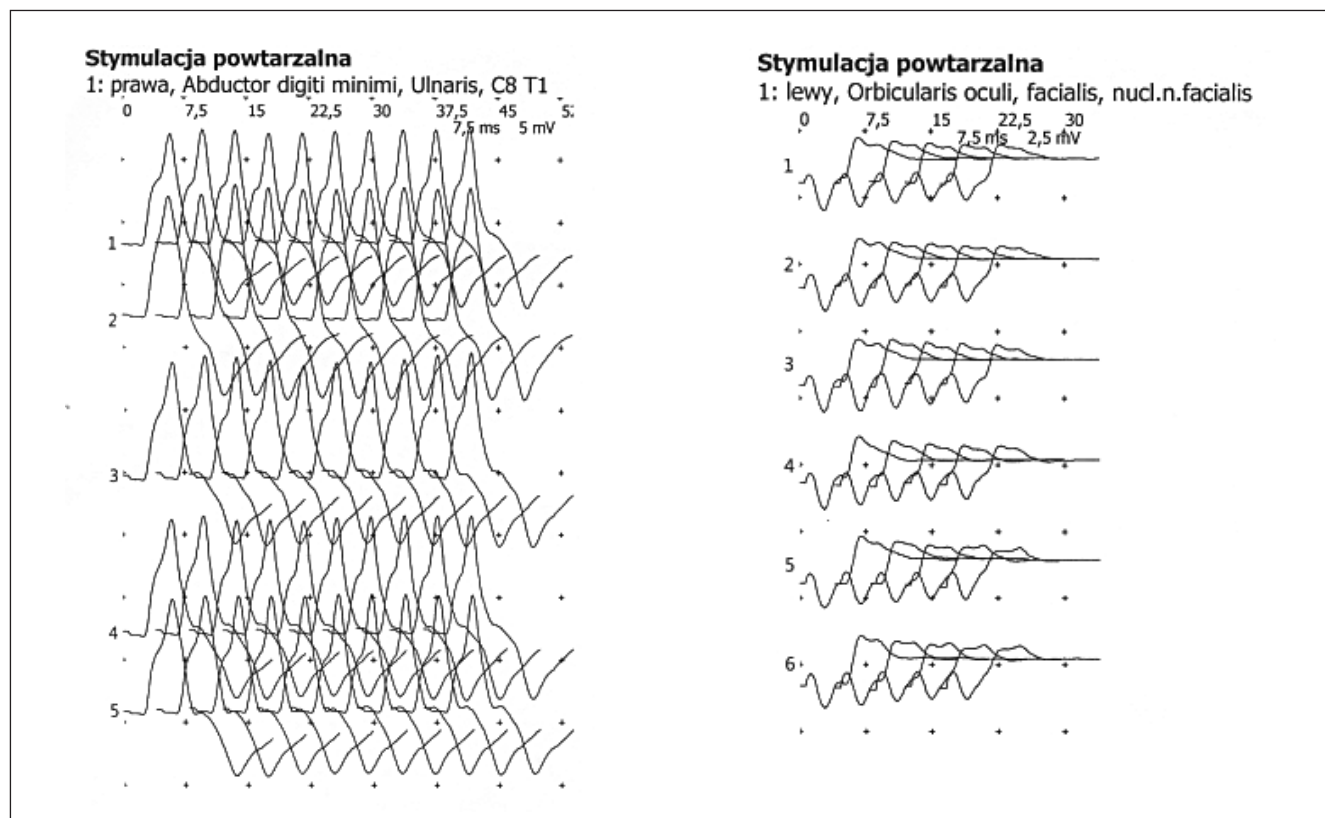


Fig. 2A. Negative result (-) of the ulnar nerve repetitive electrostimulation test

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 acetylocholin; ANA Profile = profil przeciwciał przeciwjądrowych; TSAb = przeciwciała przeciw tarczycowe stymulujące; TBAb = przeciwciała przeciw tarczycowe 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-existence 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 pyridostigmine), GD treatment (methimazole) was continued, with fluctuations of thyroid hormone levels observed

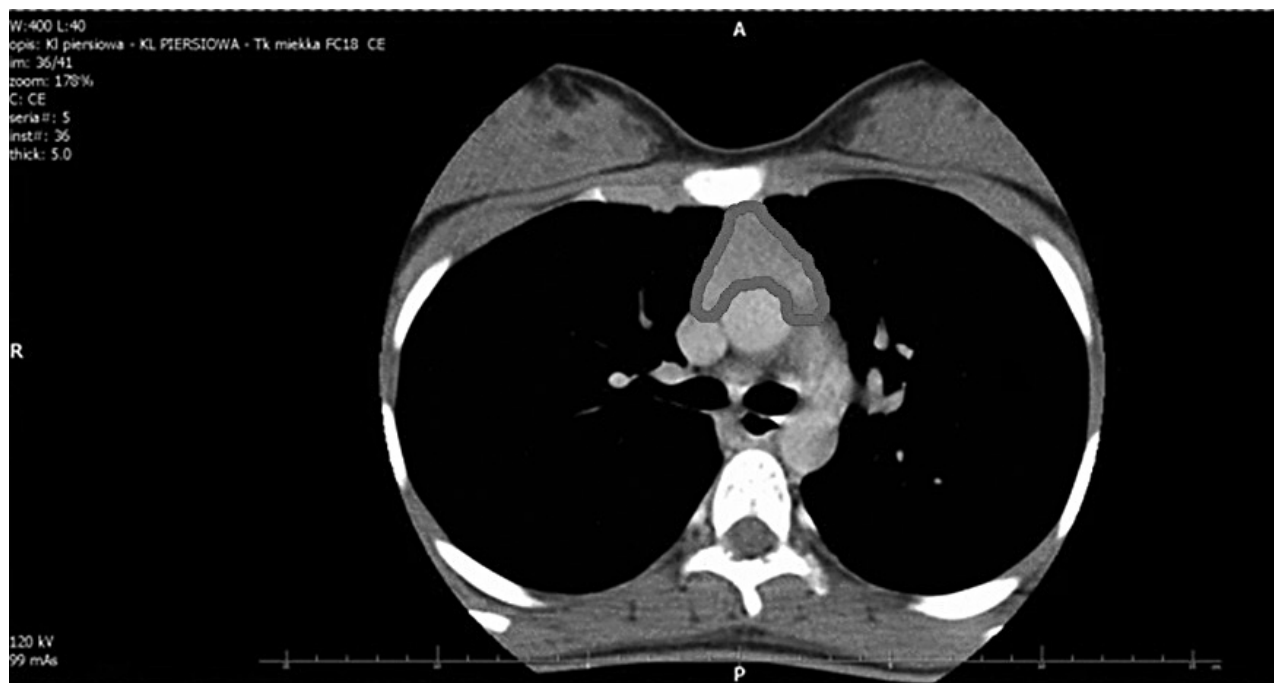


Fig. 3. Chest CT-scan showing abnormal thymus (32 x 40 mm)

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 $\geq 5,0$ WHO units/mL uznawano za dodatnie IA-2 Ab – immunoprecypitacja znakowanych 125I IA-2; wartości > 1 WHO units/mL uznawano za dodatnie Insulin Ab – immunoprecypitacja; 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 – immunoprecypitacja, znakowanie 125I; wartości $\geq 0,5$ 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 (+)

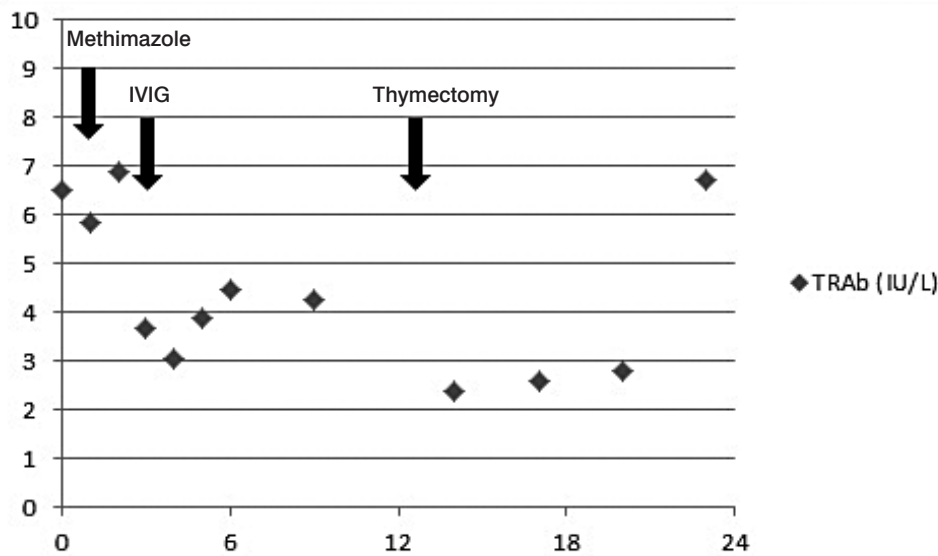


Fig. 4. TSR-Ab fluctuations depending on time (months) and the treatment applied
Ryc. 4. Wahania TSR-Ab w czasie (miesiące), w odniesieniu do zastosowanego leczenia

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 approximately 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 diag-

nosed 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.

Acknowledgements

We would like to thank dr J. Furmaniak and prof. B. Rees Smith (FIRS Laboratories, RSR Ltd, Parc Ty Glas Llanishen Cardiff, United Kingdom) for performing the organ-specific autoantibody tests.

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