ORIGINAL ARTICLE

Medycyna Ogólna i Nauki o Zdrowiu 2022, Tom 28, Nr 4, 341–344
www.monz.pl

Schmidt syndrome – is it easy to recognize? Case report

Zespół Schmidta – czy łatwo rozpoznać? Opis przypadku

Magdalena Kozioł[1,A-D], Ewa Obel[2,E-F], Aleksandra Krasa[1,A-C], Barbara Rusinowska[1,A-B], Martyna Lewkowicz[1,A-B]

[1] *Student Research Group, Endocrinology and Diabetology Clinic, Medical University, Lublin, Poland*
[2] *Department of Endocrinology and Diabetology, Medical University, Lublin, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article

Kozioł M, Obel E, Krasa A, Rusionowska B, Lewkowicz M. Schmidt syndrome – is it easy to recognize? Case report. Med Og Nauk Zdr. 2022; 28(4): 341–344. doi: 10.26444/monz/156368

Abstract

Introduction. Schmidt›s syndrome is one of the APS-2 variants, occurring with the frequency of 1.5–4.5 / 100,000, diagnosed approximately twice as often in women. Family occurrence is observed. Schmidt›s syndrome is found in the form of Addison›s disease and autoimmune thyroid disease. The units that make up the syndrome can appear in any order and time, and overlapping symptoms make diagnosis difficult.
Case Report. A 39-year-old patient with hypothyroidism and impending adrenal crisis was admitted to the Endocrinology Department for hormonal evaluation. In the history of about a year, weight loss of 20 kg, lack of appetite, weakness, hypotonia, slightly darker skin with a large number of freckles. Second amenorrhea for a year and symptoms of depression. Two weeks earlier, the patient was hospitalized in the neurology department due to confusion, hyponatremia and cerebral edema found on CT. Symptoms after administration of mannitol and hydrocortisone resolved. Moreover, the abdominal CT scan revealed hypotrophic adrenal glands. In the Department of Endocrinology, a low concentration of morning cortisol was confirmed with a high level of ACTH (1623 pg / ml), which allowed confirmation of the diagnosis of Addison's disease. In addition, Hashimoto's disease was found. The coexistence of both diseases allowed the diagnosis of Schmidt's syndrome.
Conclusions. The probability that a patient with one autoimmune disease will be diagnosed with another entity from the autoimmune spectrum is very high. The presented patient had typical symptoms of adrenal insufficiency, but they were associated with malnutrition, hypothyroidism and depression. Often, the symptoms of Addison's disease are masked by hypothyroidism, which makes diagnosis difficult.

Key words

Hashimoto's disease, Addison's disease, Schmidt's syndrome, APS-2

Streszczenie

Wprowadzenie. Zespół Schmidta to jeden z wariantów APS-2 występujący z częstością 1,5–4,5/100 tys. przypadków, ok. dwukrotnie częściej rozpoznawany u kobiet. Obserwuje się występowanie rodzinne. Zespół Schmidta jest spotykany pod postacią choroby Addisona oraz autoimmunologicznej choroby tarczycy. Jednostki wchodzące w skład zespołu mogą ujawniać się w dowolnej kolejności i czasie, a nakładające się objawy utrudniają rozpoznanie.
Opis przypadku. Pacjentka w wieku 39 lat, z niedoczynnością tarczycy oraz w stanie zagrażającego przełomu nadnerczowego została przyjęta do kliniki endokrynologii celem oceny hormonalnej. Przeprowadzony wywiad wykazał, iż w ciągu ok. roku pacjentka straciła 20 kg masy ciała, stwierdzono także brak apetytu, osłabienie, hipotonię, skórę o nieznacznie ciemniejszym zabarwieniu z dużą liczbą piegów, wtórny brak miesiączki (od roku) oraz objawy depresji. Dwa tygodnie wcześniej pacjentka była hospitalizowana na oddziale neurologii z powodu splątania, hiponatremii oraz stwierdzonego w TK obrzęku mózgu. Po podaniu mannitolu i hydrokortyzonu objawy ustąpiły. Ponadto w TK jamy brzusznej stwierdzono hipotroficzne nadnercza. W klinice endokrynologii potwierdzono niskie stężenie porannego kortyzolu przy wysokim poziomie ACTH (1623 pg/ml), co pozwoliło na potwierdzenie diagnozy choroby Addisona. Ponadto stwierdzono chorobę Hashimoto. Współwystępowanie obu jednostek pozwoliło postawić diagnozę zespołu Schmidta.
Wnioski. Prawdopodobieństwo, że u chorego dotkniętego jedną chorobą autoimmunologiczną rozpozna się inną jednostkę ze spektrum autoagresji jest bardzo duże. U naszej pacjentki występowały typowe objawy niedoczynności nadnerczy, jednakże wiązane one były z niedożywieniem, depresją oraz niedoczynnością tarczycy. Często objawy choroby Addisona są maskowane niedoczynnością gruczołu tarczowego, co utrudnia i wydłuża diagnostykę.

Słowa kluczowe

choroba Hashimoto, zespół Schmidta, choroba Addisona, APS-2

Address for correspondence: Magdalena Kozioł, Student Research Group, Endocrinology and Diabetology Clinic, Medical University, Lublin, Poland
E-mail: magdalena.koziol@icloud.com

Received: 02.11.2022; accepted: 08.11.2022; first published: 29.11.2022

INTRODUCTION

Schmidt's syndrome is one of the subtypes of the autoimmune polyglandular syndrome type 2 (APS-2). It is characterized by the presence of primary adrenal insufficiency (Addison's disease) in combination with autoimmune thyroid disease. The frequency of occurrence is estimated at 1.5–4.5 / 100,000. residents [1]. According to the literature, this syndrome is found at any age, but it is rare among children and over 60 years of age [2]. Individual diseases may appear simultaneously, but most often one of the diseases is initially diagnosed [1].

The history of the disease dates back to 1926, when Schmidt first described two patients with both primary adrenal insufficiency (Addison's disease) and autoimmune thyroid disease. Since then, such a combination has been called Schmidt's syndrome. The patients described by the researcher had no symptoms of hypothyroidism, but only a lymphocytic infiltration found in the autopsy or histopathological examination of the removed gland [3].

This phenomenon was investigated by Wells et al. on a group of 20 patients with Addison's disease. It was shown that in this group of patients, thyroid lymphocytic infiltration was much more frequent in patients with idiopathic Addison's disease than in the group with tuberculous adrenal insufficiency. Attention was drawn to the increased risk of another disease from the autoimmune spectrum [4]. APS-2 may also include type 1 diabetes mellitus – this coexistence of three disease entities is referred to as Carpenter's syndrome [5]. Less common are: primary hypogonadism, pernicious anemia, vitiligo, myasthenia gravis, alopecia areata or celiac disease [6, 7].

CASE REPORT

A 39-year-old patient with hypothyroidism of unclear etiology and adrenal crisis developing was admitted to the Department of Endocrinology for hormonal assessment, diagnosis and further treatment. In the patient's medical history a weight loss of more than 20 kg, fatigue, weakness and hypotension (including orthostatic hypotension) had been reported for about a year. In the examination, the patient's skin was dry, slightly darker in colour with a lot of freckles and pigmented lesions all over the body. In addition, edema was identified, most likely caused by protein-fat malnutrition and coexisting anemia of complex etiology due to iron deficiency and chronic diseases. Moreover, the patient complained of a lack of appetite and the desire to eat salty foods. The woman had also been diagnosed with secondary amenorrhea for about a year; however the performed hormonal profile did not correspond to the menopausal constellation. Due to hypothyroidism, the patient had been on substitution with levothyroxine at a dose of 88 µg/day for about two years, but no laboratory tests were performed during that time period. In addition, the woman had been taking antidepressants for a year due to a mood disorder. There were no reports of autoimmune diseases in the family history.

Two weeks earlier, the patient was urgently hospitalized in the neurology department due to confusion, vomiting, hyponatremia and cerebral edema found on CT. Symptoms after administration of mannitol and hydrocortisone resolved. Abdominal CT scan showed hypotrophic, atrophic adrenal glands without focal changes.

The patient had been visiting many specialists for a year, but the diagnosis was unclear. Initially, the focus was on the woman's mood disorders and amenorrhea, whereas malaise was associated with symptoms of hypothyroidism and stress. In the Department of Endocrinology, very low concentrations of morning cortisol (0.7 µg/ml) were reported with a high level of ACTH (1623 pg/ml).

Table 1. Laboratory results

Indicator name	Results – first day of hospitalization	Results – last day of hospitalization
RBC	3.25 mln/mm^3 ↓	
EOS %	6.7% ↑	
MCV	92.4 fl	
HGB	9.7mmol/l ↓	
HCT	30.1% ↓	
WBC	6.09 tys./µL ↑	
Kalium	3.6 mmol/l	5.1mmol/l
Natrium	144 mmol/l	143mmol/l
Urea	50.1 mg/dl↑	38mg/dl
Glucose	84.0 mg/dl	
Total protein (blood)	4.0 g/dl↓	6.6 g/dl
Albumin	2.61 g/dl↓	4.29 g/dl
Total cholesterol	154 mg/dl	
HDL cholesterol	59 mg/dl	
LDL cholesterol	69 mg/dl	
Triglycerides	128 mg/dl	
TSH	6.98 mIU/L↑	
fT3	1.8 pg/ml↓	
fT4	0.87 ng/ml↓	
Iron	28 ug/dl↓	
Transferrin	171.0 mg/dl↓	
Ferritin	42 ng/ml	
IgA	88.0 mg/dl	
Anti-transglutaminase antibodies (anti-tTG)	<1.9 CU - Negative	
Anti-endomysial antibodies IgA	Negative	
Anti-endomysial antibodies IgA	Negative	
ATG	22.0 U/ml	
ATPO	2,059.30 U/ml Positive	
Anti-21-hydroxylase antibodies	Positive	
Cortisol	0.7 µg/ml ↓	41.7 µg/ml
ACTH	1,623.0 pg/ml↑	
The oral iron absorption test		
0′	1h′	2h′	5h′
45.0 µg/dl	120.0 µg/dl	231.0 µg/dl	208.0 µg/dl

The clinical symptoms in combination with the results of laboratory tests allowed for unequivocal confirmation of the diagnosis of primary adrenal insufficiency – Addison's disease. In addition, positive titers of antibodies were confirmed: anti-21-hydroxylase antibodies and anti-peroxidase (anti-TPO). Celiac disease was excluded – no anti-transglutaminase antibodies in class I and anti-endomysial antibodies were found. Moreover, no features characteristic of pernicious anemia were observed.

Based on the clinical picture and the performed tests, the diagnosis of Addison's disease with autoimmune causes and autoimmune thyroiditis (Hashimoto's disease) was made. The combination of these two disease entities in one patient allowed for the diagnosis of Schmidt's syndrome.

It is worth mentioning that substitution of levothyroxine in patients with untreated primary adrenal insufficiency may cause adrenal crisis, as it increases hepatic metabolism of corticosteroids [6]. Therefore, in this case, the L-thyroxine substitution was discontinued and substitution with hydrocortisone at a dose of 100 mg was started by an intravenous injection, followed by 100 mg per day as an infusion. After the patient's condition had normalized, the substitution of L-thyroxine was added to the treatment, again at a dose of 88 μg/d. The treatment with oral hydrocortisone at a dose of 20 mg in the morning and 10 mg at noon was continued. The applied treatment contributed to the improvement in the general and mental condition of the patient, enabling the discontinuation of antidepressants. Moreover, as a result of compensating for nutritional deficiencies and increasing body weight, the normalization of sex hormones to the levels corresponding to the follicular phase was observed. Therefore, the patient's regular menstrual cycles were reclaimed. The patient was instructed of the necessity to increase the dose of hydrocortisone in stressful situations.

DISCUSSION

Schmidt›s syndrome consists of many symptoms, including: fatigue, eating disorders, dizziness, pain in muscles and joints, decreased libido [5, 8]. Psychiatric symptoms are also often described, including mood disorders and productive symptoms, e.g. delusions [9, 10]. Depression has been repeatedly described as the first symptom in patients with Addison›s disease. Glucocorticoid deficiency, electrolyte and metabolic disturbances are recognized as probable causal mechanisms of psychiatric symptoms related to the disease [9], as in the case of a 64-year-old woman with generalized anxiety described by D. Anyfantakis et al. Mental deterioration and depression were associated with stress and increasing socio-economic problems of the woman. Monthly treatment with antidepressants did not produce any results, on the contrary – the patient was admitted to the ward with significant signs of dehydration, discolouration of the skin of the elbows and knees. The performed tests allowed for establishing the diagnosis [11].

In the described patient, the onset of Addison›s disease had a typical course – loss of appetite, weight loss, desire for salty foods, weakness, fatigue along with a depressed mood. However, there are cases where there are no specific symptoms. Bain A et al. presented the case of a patient with Schmidt›s syndrome, the onset of which was slow and the typical weight loss was not observed. The authors emphasized the fact that the diagnosed hypothyroidism may mask the symptoms of the new disease, extending the diagnostic process. On the other hand, a very rapid onset leading to an adrenal crisis may be induced by bacterial or viral infections, surgery or trauma [1].

The literature also describes cases where Addison›s disease is the first to appear. Such a situation occurred in a woman described by Claudia Barreda-Velit et al. A patient with Addison›s disease came to the emergency room due to a nausea, vomiting, headache and fainting episode. A history of secondary amenorrhea, osteoporosis and weight loss was reported. The woman was admitted to the hospital in a serious condition because the overlapping symptoms and the onset of another autoimmune disease that affected the thyroid gland were not recognized. The panel of performed tests, including antibodies, allowed for the diagnosis of Schmidt›s syndrome [12].

Another example confirming the overlapping of symptoms is the case of the patient with premature cessation of ovarian function described by Amit Narayan Gupta et al. Clinical symptoms that suggested meningitis actually masked symptoms of corticosteroid deficiency. The woman underwent several courses of antibiotic therapy, which did not bring the expected improvement in health. After six months of improper therapy, the patient developed hypotension, body discolouration, weight loss and anorexia. The hormonal tests allowed for the diagnosis [13].

Secondary amenorrhea is a very common abnormality among women suffering from Schmidt›s syndrome. Most often it occurs simultaneously with other symptoms. The detected hypergonadotropic hypogonadism is recognized as a symptom of early menopause; however, as a result of correct treatment of Schmidt›s syndrome, normal menstrual cycles return [12]. An example confirming the presence of secondary amenorrhea in the course of this syndrome is the case of the patient described by Gaba N et al. A 36-year-old woman was diagnosed with anorexia, nausea, excessive fatigue, skin discolouration and weight loss. Over the course of several months, her symptoms gradually worsened to the point that she was unable to carry out daily activities on her own. However, after the treatment, the general condition improved significantly and normal menstrual cycle returned [14]. A similar situation was described by Aasem Saif et al. in which the authors presented a patient who was initially diagnosed with premature ovarian failure. However, the conducted research allowed for the diagnosis of Schmidt›s syndrome [15]. This disease reduces the ability to have children and it is difficult to maintain a pregnancy [16].

An example confirming the increased risk of developing another autoimmune disease is the case described by Bonnie Stahn et al. [17]. A 22-year-old man visited his doctor because of exhaustion, changes in skin colour, and significant weight loss. Hashimoto›s disease was present in his medical history. Fatigue, weakness and edema were associated with the intensification of symptoms of hypothyroidism. However, gradually increasing the dose of levothyroxine did not produce the expected effect. The performed diagnostics allowed identification of the presence of antibodies against the adrenal cortex and a low level of cortisol. On this basis, the diagnosis of Addison›s disease was made, and then Schmidt›s syndrome.

The presented case highlights the fact that it is easy to overlook the symptoms of the initial stage of another autoimmune disease. An excessively long diagnostic process may lead to serious electrolyte disturbances, such as severe hyponatremia [18] and a life-threatening adrenal crisis [19], which may result in the death of the patient [20]. It is noteworthy that the quick administration of hydrocortisone at the time of adrenal crisis allows inhibition of the brain edema and stabilization of the patient›s clinical condition, as in the case of the patient described. The finding of severe

hyponatraemia should always be an indication for the differential diagnosis of Addison›s disease [18].

The family history of autoimmune diseases has been proven. It has been found that the genes responsible for the occurrence of this disease are located in particular on chromosome 6 [21]. Given the high prevalence of one or more endocrinopathies in first degree relatives of APS-2 patients, family members should be screened regularly [6].

CONCLUSIONS

The components of Schmidt›s syndrome may show up at different times, even many years after the first diagnosis. Hypothyroidism in the course of autoimmune thyroiditis is a relatively common disease and its symptoms overlap with newly-developing Addison›s disease. A too superficial examination may cause diagnostic errors and the initiation of L-thyroxine treatment may lead to symptoms of adrenal crisis. As can be seen from the cases presented above – among patients with diagnosed autoimmune disease, it is recommended to conduct control tests for other diseases of autoimmune etiology. The presence of autoimmune diseases in a family should also encourage proper diagnosis among first-degree relatives who present non-specific symptoms.

REFERENCES

1. Bain A, Stewart M, Mwamure P, et al. Addison›s disease in a patient with hypothyroidism: autoimmune polyglandular syndrome type 2. BMJ Case Rep. 2015; 2015:bcr2015210506. doi: 10.1136/bcr-2015-210506
2. Resende E, Gómez GN, Nascimento M, et al. Precocious presentation of autoimmune polyglandular syndrome type 2 associated with an AIRE mutation. Hormones (Athens). 2015;14(2):312–6. doi:10.14310/horm.2002.1513
3. Schmidt MB. Eine biglandulare Erkrankung (Nebennieren und Schilddrüse) bei Morbus Addisonii. Verh Dtsch Ges Pathol 1926;21:212–21
4. Wells HG. Addison›s disease with the selective destruction of the suprarenal cortex. Arch Pathol. 1930;10:499–523.
5. Smith RK, Gerrits PM. A Rare Case of Autoimmune Polyglandular Syndrome Type 2 in a Child With Persistent Fatigue. Glob Pediatr Health. 2019;1;6:2333794X19845074. doi: 10.1177/2333794X19845074
6. Kahaly GJ, Frommer L. Autoimmune polyglandular diseases. Best Pract Res Clin Endocrinol Metab. 2019;33(6):101344. doi: 10.1016/j.beem.2019.101344
7. Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest. 2018;41,91–98. https://doi.org/10.1007/s40618…
8. Schulz L, Hammer E. Autoimmune polyglandular syndrome type II with co-manifestation of Addison›s and Graves› disease in a 15-year-old boy: case report and literature review. J Pediatr Endocrinol Metab. 2020;28;33(4):575–578. doi: 10.1515/jpem-2019-0506
9. Anglin RE, Rosebush PI, Mazurek MF. The neuropsychiatric profile of Addison›s disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci. 2006;18(4):450–9. doi: 10.1176/jnp.2006.18.4.450
10. Patel DM, Gurumikhani JK, Patel MV, et. al. Adrenocortical Crisis Triggered by Levothyroxine in an Unrecognized Autoimmune Polyglandular Syndrome Type-2: A Case Report with Review of the Literature. Curr Drug Saf. 2021;16(1):101–106. doi: 10.2174/1574886315666200826095842
11. Anyfantakis D, Symvoulakis EK, Vourliotaki I, et al. Schmidt's syndrome presenting as a generalised anxiety disorder: a case report. J Med Life. 2013;6(4):451–3.
12. Barreda-Velit C, Salcedo-Pereda R, Ticona J. Síndrome de Schmidt: diagnóstico difícil en el contexto latinoamericano [Schmidt's syndrome: a difficult diagnosis in the Latin American context]. Rev Med Inst Mex Seguro Soc. 2018;56(2):189–193.
13. Gupta AN, Nagri SK. Schmidt's syndrome – Case report. Australas Med J. 2012;5(6):292–5. doi: 10.4066/AMJ.2012.987
14. Gaba N, Gaba S, Singla M, et. al. Type 2 Autoimmune Polyglandular Syndrome Presenting with Hyperpigmentation and Amenorrhea. Cureus. 2020;12(4): e7772. doi: 10.7759/cureus.7772
15. Saif A, Assem M. Premature ovarian failure could be an alarming sign of polyglandular autoimmune dysfunction. Endocr Regul. 2017;25;51(2):114–116. doi: 10.1515/enr-2017-0011
16. Yanachkova V, Chaveeva P, Staynova R, et al. Autoimmune Polyglandular Syndrome Type 2 and Pregnancy. Folia Med (Plovdiv). 2020;30;62(2):408–411. doi: 10.3897/folmed.62.e48580. PMID: 32666756
17. Stahn B, Scheit L. Das Schmidt-Syndrom [The Schmidt's Syndrome]. Dtsch Med Wochenschr. 2019;144(24):1741–1744. doi: 10.1055/a-0875-4538. PMID: 31791082
18. Wiśniewski OW, Matuszak P, Kasprzak A, et al. Severe hyponatremia as the first sign of late-onset Schmidt's syndrome: A case report. Caspian J Intern Med. 2021;12(Suppl 2):S392-S396. doi: 10.22088/cjim.12.0.392
19. Wang X, Ping F, Qi C, Xiao X. Delayed diagnosis with autoimmune polyglandular syndrome type 2 causing acute adrenal crisis: A case report. Medicine (Baltimore). 2016;95(42):e5062. doi: 10.1097/MD.0000000000005062
20. De-Giorgio F, Foti F, Bergamin E, et al. Regarding „Fatal adrenal crisis due to Addison›s disease arising in the context of autoimmune polyglandular syndrome type 1". Forensic Sci Med Pathol. 2022;18(2):226–227. doi: 10.1007/s12024-021-00439-0
21. Flesch BK, König J, Frommer L, et al. Gender alters the MHC class I HLA-A association with polyglandular autoimmunity. J Clin Endocrinol Metab. Figshare 2018. Deposited 25 October 2018. https://doi.org/10.6084/m9.figshare.7251704.v1