



# Schmidt syndrome mimicking depression and refractory hypotension in critically ill patient – Case Report and Literature Review

Joanna Chajec<sup>1,A-D</sup>✉, Paweł Kutnik<sup>2,E-F</sup>

<sup>1</sup> Student Scientific Association, Second Department of Anesthesiology and Intensive Therapy, Medical University, Lublin, Poland

<sup>2</sup> Second Department of Anesthesiology and Intensive Therapy, Medical University, Lublin, Poland

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## Abstract

Schmidt syndrome is a disorder of the endocrine system associated with both autoimmune thyroid disease and primary adrenal insufficiency. Nondistinctive nature and delayed appearance of the symptoms are difficult to diagnose. Moreover, an untreated adrenal insufficiency crisis may lead to a life-threatening condition requiring rapid treatment, which includes corticosteroids supplementation. We present a case of a 21-year-old male, with a history of thyroid disorder and depression, who was admitted to the intensive care unit due to COVID-19 with circulatory insufficiency including persistent hypotension and electrolyte imbalances. The patient was diagnosed with Schmidt syndrome and proper treatment was implemented. Although Schmidt syndrome is a rare condition, appropriate diagnosis is a key to introducing proper treatment, which despite being a lifetime commitment, can resolve all the symptoms.

## Key words

depression, Schmidt syndrome, APS2

## INTRODUCTION

Autoimmune polyendocrine syndrome type 2 (APS2) is a rare autoimmune disorder most often characterized by the presence of primary adrenal insufficiency, also known as Addison's disease (AD), autoimmune thyroid disease and/or type 1 diabetes. APS2 occurs with a frequency of 1:20 000 [1]. Although APS2 consists of at least two endocrinopathies, the onset of each of them reportedly can take part independently in more than 20 years gap. [2] Early manifestations of Addison's disease are often non-specific and can mimic other disorders, for example, gastrointestinal disorder or psychiatric disease, depression in particular. The frequent underdiagnosis in the early stages results in potentially life-threatening consequences of the disease [3].

Schmidt syndrome is an APS2 endocrinological disorder with two components – autoimmune thyroid disease and AD. Half of the cases of thyroid disease linked to APS2 are Grave's disease, and the other 50% are either Hashimoto's or atrophic thyroiditis. [4] Most often it occurs in adults between the ages of 20 and 60, primarily in the third or fourth decade, however, it may be rarely seen in childhood. It is 3 times more often encountered in females than males [5]. Due to overlapping general symptoms of hypothyroidism and adrenal insufficiency, the diagnosis at early stages might remain a challenge to clinicians. Although thyroid conditions are often caught and treated by primary care physicians, the AD component usually becomes detected during significant

stress or illness [6]. Patients' medical history can have some clues regarding potential APS2 syndrome.

Herein we present a case of a 21-year-old male, previously treated for hypothyroidism and depression, who was admitted to the ICU with COVID-19 infection due to refractory hypotension and electrolyte imbalances.

## CASE REPORT

A 21-year-old male patient with a history of primary hypothyroidism and depression was transferred to the Intensive Care Unit (ICU) from the Infectious Diseases Department of the same hospital, where he was hospitalized due to SARS-CoV-2 infection. The patient had been treated for hypothyroidism for two years and one year for depression, receiving levothyroxine and sulpiride. Prior to the admission, the patient had withdrawn twice from exam sessions at universities, always presenting symptoms of depression, including lack of energy, the need to stay in bed for the entire day, and anhedonia. On admission to the ICU, the patient presented persistent hypotension requiring continuous noradrenaline (0.28 ug/kg/min) to maintain systolic blood pressure over 90 mmHg, and electrolyte disturbances (Tab. 1).

On admission to the ICU, the patient was agitated, with limited logical contact, and skin irritation. He required occasional sedation with diazepam, hydroxyzine and propofol due to the agitation, but on other occasions, the onset of lethargy required a sudden withdrawal of all sedative medications. The respiratory system was mildly affected, requiring a nasal cannula with 3l/min flow to maintain saturation between 94–98%. An insufficient circulatory system was supported with crystalloid fluids

✉ Address for correspondence: Joanna Chajec, Student Scientific Association, Second Department of Anesthesiology and Intensive Therapy, Medical University of Lublin, Poland  
E-mail: asiach16185@gmail.com

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**Table 1.** Patient's laboratory results on admission to ICU and the day after receiving the first steroid treatment

Laboratory test	Results on admission	Results on day after administration of glucocorticosteroids	Ref. range
Sodium [mmol/l]	124	139	136–145
Potassium [mmol/l]	6.95	4.48	3.5–5.1
Chloride [mmol/l]	89.7	104	98–107
Calcium [mmol/l]	2.47	2.28	2.15–2.5
Magnesium [mmol/l]	0.78	0.72	0.66–1.07
Phosphate [mmol/l]	1.68	1.34	0.84–1.45
ACTH [pg/ml]*	1407.00	-	7.2–63.6
Free serum cortisol [nmol/l]*	1.8	-	37–194
TSH [uU/ml]	12.27	-	0.27–4.2
Ft4 [pmol/l]	13.8	-	9–20
hemoglobin	12.4	9.9	13–18
Fibrinogen [g/l]	4.5	-	2–3.9
PT [sec]	14.2	12	9.2–13.8
INR	1.23	1.04	0.8–1.2
APTT [sec]	42.9	26	25–37

\*results obtained later during the patient's stay in the ICU

ACTH – adrenocorticotropic hormone; TSH – thyroid-stimulating Hormone; Ft4 – free thyroxine; PT – prothrombin time; INR – international normalized ratio; APTT – activated partial thromboplastin time

and noradrenaline drips. There was no obvious deviation in the physical examination. The diuresis was 2 ml/kg/h due to intensive fluid therapy to maintain appropriate blood pressure. Despite the fluid and catecholamines treatment, the patient's systemic vascular resistance index remained below the reference range system and was still insufficient.

Due to electrolyte imbalance, persistent hypotension and altered consciousness, adrenal insufficiency was suspected. Laboratory tests revealed an elevated adrenocorticotropic hormone (ACTH) serum and cortisol level below the normal morning range [Tab. 1], which enabled to establish the diagnosis of primary hypocorticism. The patient's primary hypocorticism combined with hypothyroidism met the diagnostic criteria for Schmidt syndrome.

Hydrocortisone was included, initially 50 mg i.v. every 6 hours, after 2 days reduced to 50 mg i.v. every 8 hours, and after another 2 days replaced by 30mg+10mg+10mg scheme of hydrocortisone and 0,05 mg of fludrocortisone acetate orally. Over the course of the next 4 days in the ICU, the patient's systemic vascular resistance index improved, the noradrenaline drip was discontinued, and the electrolyte disturbances resolved. The patient became more conscious and reported self-observed improved well-being. He was transferred to the Endocrinology Department for further diagnostics and treatment. Three months after discharge from the ICU, the patient discontinued anti-depressants and planned to reapply to university.

## DISCUSSION

According to a population-based cohort study conducted by Conrad et al. [7], autoimmune diseases affect around 10% of people. Nationwide studies from various European countries reveal an even bigger percentage of autoimmune diseases particularly coexisting with autoimmune Addison's disease

(AAD). In Norway, comorbid autoimmune thyroid disease was diagnosed in 48% of AAD patients, in Sweden it was around 47%, while an Italian study reports a 68% coexistence. The high rate in Italy can be associated with the inclusion of patients with normal thyroid function in laboratory tests, but thyroid autoantibodies and an ultrasound pattern suggesting thyroiditis. It is also worth mentioning that the debut of hypothyroidism was reported in 49% of the patients in Italy, prior to the onset of AAD [8, 9, 10].

Due to the relatively rare prevalence of Schmidt syndrome, appropriate diagnosis remains a challenge to clinicians. Inadequate or untreated AAD causes TSH levels to rise, which may result in an over-diagnosis of hypothyroidism [11, 12]. As previously mentioned, AD can present as a psychiatric disorder, especially depression, which makes finding the proper diagnosis more challenging [13, 14]. In the case of the presented patient, both hypothyroidism and depression could explain the symptoms that the patient was presenting before contracting COVID-19 and admission to ICU. Thus, screening for rare APS2 was not performed by the treating physicians. However, untreated adrenal insufficiency can lead to adrenal crisis which is a life-threatening condition, especially among young men [15].

Schmidt syndrome can be challenging to diagnose, but there are some indications that we should be aware of. To begin with, in the presented case report the patient had a history of autoimmune thyroid disease, which draws attention to a wide group of other autoimmune diseases. A tendency to develop additional autoimmune diseases is seen in about 25% of patients with autoimmune disorders [16]. Despite the hypothyroidism treatment with levothyroxine, according to the patient's medical records, the TSH level was increasing, which is common in APS2 where adrenal insufficiency should be treated at least for a week before introducing the hypothyroidism treatment [17].

Another aspect to discuss is resistance to treatment, which again drew our attention to seek the cause of the patient's condition. Thyroid disorders are usually associated with the development of secondary hypertension, yet in the presented patient, we were observing hypotension refractory to standard treatment [18]. This was the main reason for admission to the ICU. In this case, an insufficient circulatory system could be one of the signs of an Addisonian crisis [19]. The patient in this case report required a substantial dose of noradrenaline infusion to maintain systolic blood pressure over 90 mmHg, despite a relatively mild onset of COVID-19. In the past, the patient reported similar lethargy symptoms when exposed to stress or illness, including catching a cold or preparing for a university examination.

Last, but not least, the patient's electrolyte imbalances were not connected with increased diuresis. Elevated potassium and decreased sodium are more common for renal failure and decrease in urine output, but also the symptoms of adrenal insufficiency. In the presented case, COVID-19 did not severely affect the patient's respiratory system, and proper oxygenation could be maintained with nasal cannulas and low oxygen flow. The patient also did not present shortness of breath, tachypnoea or auscultatory signs. Thus, the symptoms of COVID-19 were not in conjunction with other symptoms the patient presented.

With all the above information, tests were carried out for adrenal insufficiency which was confirmed by elevated ACTH and decreased cortisol serum levels. Due to the introduced

treatment, noradrenaline infusion could be stopped, and the dissolution of disturbances in electrolytes was observed.

Although some published cases describe COVID-19 infection as a direct trigger for Addison's disease [20, 21], the authors of this case report believe that the patient suffered from Schmidt syndrome before contracting COVID-19. Yet, COVID-19 was a strong enough infection to require hospital admission and allowed us to extend the patient's diagnosis. In the case of the presented patient, the steroid supplementation allowed the majority of the patient's symptoms to be resolved. After 3 months of treatment and consultation with a psychiatrist, the patient discontinued antidepressants as he no longer required them. The patient decided to reapply to university and give it another try.

## CONCLUSIONS

Schmidt syndrome is a rare autoimmune disorder that can mimic other more common diseases. It can affect the course of illness or other diseases creating therapeutic difficulties. Although Schmidt syndrome is relatively rare, it should be remembered as a differential diagnosis, in refractory to the treatment of depression. Appropriate diagnosis is a key to introducing proper treatment which, although being a lifetime commitment, can resolve all the symptoms.

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