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Rare clinical problem — isolated ACTH deficiency associated with chronic alcohol abuse

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Abstract

Isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) is a rare pituitary disorder characterized by decreased secretion of ACTH, leading to cortisol deficiency, with normal secretion of other pituitary hormones. Diagnostics remains a challenge due to variable and non-specific clinical presentation: weakness, weight loss, and low blood pressure. Hyponatremia and anemia are typical abnormalities in basic laboratory tests. Diagnostic procedures for IAD are based on results of low morning cortisol with low/normal ACTH concentrations, with flat response of these hormones in dynamic tests [with insulin/glucagon/corticotropin-releasing hormone (CRH)]. There is also no cortisol response to Synacthen during the standard (not extended) test duration. Several aetiologies lead to the development of IAD. The congenital form is typical of childhood onset. In adults, autoimmune aetiology prevails, including lymphocytic hypophysitis, and rarer — pituitary injury or other lesions in the gland. IAD has recently been demonstrated as a complication in patients receiving therapy with immune checkpoint inhibitors. Also, in the case of IAD, paraneoplastic autoimmune hypophysitis should be considered. Next, alcohol abuse has been reported to be a reason of IAD in single cases. Treatment with oral hydrocortisone usually causes significant improvement. As an example, we present 2 patients diagnosed with IAD. Both were older males, with history of alcohol abuse, long lasting hyponatremia, and weakness. Their clinical state normalized after receiving replacement therapy with hydrocortisone. **(Endokrynol Pol 2022; 73 (4): 778–783)**

Key words: *isolated ACTH deficiency; alcohol abuse; secondary adrenal failure; hyponatremia*

Introduction

Definition of IAD

Isolated adrenocorticotropic hormone deficiency (IAD) is a rare pituitary disorder characterized by decreased secretion of adrenocorticotropic hormone (ACTH) and consequently lowered cortisol level, with normal pituitary structure and preserved secretion of other pituitary hormones [1, 2]. An important element in the definition of IAD is the primary nature of ACTH deficiency, in contrast to more frequent iatrogenic conditions, in which ACTH is suppressed by prolonged glucocorticoid administration [2].

Symptoms of IAD

Common clinical symptoms are not characteristic and include fatigue, weakness, anorexia, weight loss, nausea, vomiting, and low blood pressure. Non-specific presentation hinders and delays proper diagnosis [2, 3]. Some patients are not diagnosed until they develop an adrenal crisis. Typical abnormalities, found in basic laboratory tests, are anemia (less often — lymphocytosis and eosinophilia) and hyponatremia. However, IAD seems to be a rare cause of hyponatremia. In one of the larger clinical studies, in a group of 185 patients with severe hyponatremia (< 130 mmol/L) only 28 had secondary adrenal insufficiency, but most of them had also deficiencies of other pituitary hormones [4]. The mechanism of hyponatremia in IAD includes a reduced glomerular filtration rate and ineffective inhibition of vasopressin secretion caused by hypocortisolaemia [2, 5]. Because IAD is not associated with deficiency of aldosterone, the mechanism of salt-wasting is less important [2].

Diagnosis of IAD

Diagnostic procedures for IAD should start from assessment of morning cortisol concentrations. Results lower than 3.0 μg/dL, accompanied by low ACTH level, are indicative for IAD [2]. When cortisol is in the range 3.0–10.0 μg/dL, dynamic stimulatory tests [with insulin, glucagon, corticotropin-releasing hormone (CRH), or tetracosactide] are recommended [2, 3]. It should be stressed that there is also no cortisol response to Synacthen in the secondary adrenal insufficiency if the standard (not extended) test duration is used. In Poland

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a metyrapone test is employed less frequently. The traditional cut-off value of cortisol concentration allowing for a good separation between healthy individuals and patients with IAD is 18.0 μg/dL [1–3]; however, the choice of optimal test is still a matter of debate.

Aetiology of IAD

Several aetiologies lead to the development of IAD. The congenital or acquired forms are distinguished [1]. The congenital form is typical of childhood-onset IAD. It results from mutations in the proopiomelanocortin (POMC) gene or in the pituitary restricted T-box transcription factor (*TBX19*) gene [6]. In adults, the acquired form of IAD is predominant. Its pathogenesis is unclear; however, most cases are related to autoimmunity against corticotrophs [7], including lymphocytic hypophysitis. In a study of 46 patients with IAD, 58% showed antibodies against corticotropic cells and 6% demonstrated anti-follicular stellate cell (FSC) antibodies [8]. Recently, a case of IAD as a form of paraneoplastic syndrome has been reported [9]. According to this concept, the ectopic expression of pituitary antigens present in tumours evokes a breakdown of immune tolerance, resulting in the production of autoantibodies (anti-PIT1), which are a marker of the disease and can harm pituitary cells. A similar mechanism of enhanced immune response was suggested as a reason for IAD reported in patients treated for cancer with use of monoclonal antibodies directed against immune checkpoint inhibitors (most frequently — nivolumab or pembrolizumab) [10]. In retrospective analysis, the prevalence of IAD as a side-effect was about 1% of treated patients, diagnosed at a median of 7.0 months after starting immunotherapy, with 6.0 months of median overall survival since IAD diagnosis [10]. The other causes of IAD include pituitary trauma [2], primary empty saddle [11], and cases of possible "exhaustion" of central CRH/ACTH resources, resulting in secondary adrenal insufficiency [12]. Several cases of IAD related to chronic alcoholism were also described [13–15]. In some cases, the aetiology remains unknown. Long-term replacement therapy with glucocorticoids is required.

Therapy of IAD

In chronic treatment most patients need daily about 20 mg of hydrocortisone, given orally in 2 doses of 10 mg (08.00 a.m., 02.00 p.m.) to mimic the normal circadian rhythm of cortisol. Higher doses of steroids, administered intravenously, are indicated in patients who develop adrenal crisis. Mineralocorticoid substitution is not necessary, because — as mentioned before — aldosterone synthesis is not generally affected, being primarily regulated by the renin–angiotensin system [16].

We describe 2 patients with a history of alcohol abuse, suffering from weakness, weight loss, low blood pressure, and severe hyponatremia caused by IAD.

Case presentation

Patient 1

A 65-year-old male was admitted to the Department of Endocrinology PMMH-RI, for diagnostics of severe, chronic, symptomatic hyponatraemic hypotonia. He complained of general weakness and chronic nausea. His medical history included alcohol abuse, cachexia, hiatus hernia, and Barret's oesophagus. During the preceding 2 years, the patient had been hospitalized 8 times for recurrent hyponatremia (Fig. 1), accompanied by normokalaemia, mild hypomagnesemia, and chronic anemia. During his stays in the hospital, the hyponatremia had been corrected each time with saline infusions and intensive meal salting. Despite such treatment, sustainable normalization of serum sodium concentration had not been achieved. Renal diseases, liver and cardiac failure, and hypothyroidism were excluded; at the same time, the patient denied taking medications that might cause hyponatremia. Moreover, multiple abdominal and chest computed tomography (CT) and abdominal ultrasound (US) examinations excluded the presence of neoplasms, including those potentially causing SIADH. Finally, due to suspicion of an endocrine background of the patient's problems, he was referred to the Department of Endocrinology. On admission, he presented low blood pressure (RR: 100/70 mm Hg), pale skin, and low BMI (19.6 kg/m^2). Basic laboratory tests confirmed hyponatremia with normokalaemia, with urine osmolality above 100 mOsm/kg H_20, low serum osmolality, and normochromic anemia (Tab. 1). Based on extremely low cortisol concentration at 08.00 a.m. (Tab. 2), not increasing after CRH injection (100 μg IV) (Tab. 3), accompanied by low-normal ACTH and normal concentrations of the remaining pituitary hormones (Tab. 2), diagnosis of IAD was established. Additionally, low DHEAS, vitamin D, and normal levels of aldosterone and renin were found (Tab. 2). On MRI, the pituitary gland was normal with no widening or deviation of the stalk, and there were no neoplastic or inflammatory lesions. Coexisting autoimmune disorders were excluded (antithyroid and anti-adrenal antibodies were negative). Antibodies against the pituitary autoantigens were not available. Genetic analysis of the *TBX19* gene was not performed due to the late onset of ACTH deficiency. The patient was treated with hydrocortisone, 10 mg orally, twice daily (08.00 a.m. and 02.00 p.m.), with clinical and biochemical improvement, i.e. normalization of blood pressure and sodium concentration (Fig. 1).

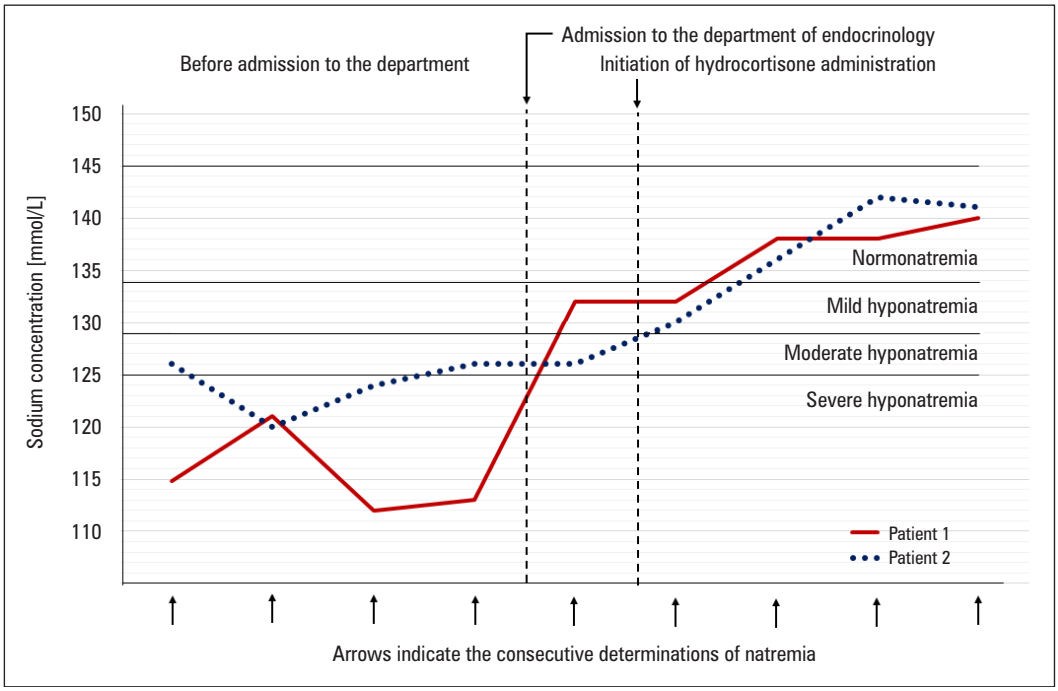

Figure 1. *Changes in sodium concentration in the presented patients before and during hospital stay, after starting hydrocortisone administration*

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Table 1. *Laboratory results at the beginning of diagnostics*

Measurement	Reference range	Patient 1	Patient 2
Sodium [mmol/L]	137–145	132	126
Potassium [mmol/L]	3.5–5.1	4.6	4.63
Magnesium [mmol/L]	0.7–1	0.63	–
Total calcium [mmol/L]	2.1–2.55	2.37	2.31
Chlorides [mmol/L]	98–107	94	–
Red blood count [$10^6/\mu L$]	4.5–6.5	3.50	3.03
Haemoglobin [g/dL]	13–18	10.7	9.4
Mean corpuscular volume [fl]	82–94	84.0	88.0
White blood count [$10^3/\mu L$]	4–10	5.69	4.50
Platelets [$10^3/\mu L$]	150–400	258	222
Aspartate transaminase [U/L]	17–59	28	39
Alanine transaminase [U/L]	< 50	8	32
Alkaline phosphatase [U/L]	38–126	42	70
Bilirubin [mg/dL]	0.2–1.3	0.43	0.37
Creatinine [mg/dL]	0.66–1.25	0.57	0.44
γ-glutamyl transpeptidase [U/L]	15–75	19	–
Urine osmolality [mOsm/kg H_2O]	500–800	377	–
Plasma osmolality [mOsm/kg H_2O]	280–300	277	–

Patient 2

A 68-year-old male noticed weakness and a gradual loss of weight of about 10 kg, as well as low blood pressure, the symptoms which progressed for about 1.5 years. Earlier he had felt completely healthy, with a past history of smoking and alcohol drinking. He had been hospitalized several times due to suspicion of neoplastic disease. On admission, the patient was pale

Table 2. *Results of hormonal examinations in the presented patients during hospital stay*

Measurement	Reference range	Patient 1	Patient 2
Cortisol at 8.00 AM [μg/dL]	5-19	1.1	0.6
ACTH at 8.00 AM [pg/mL]	10-60	16.0	5.1
DHEA [μg/mL]	51-295	13.73	31.62
Aldosterone [ng/dL] in lying position	3-16	4.08	–
Renin [mIU/mL] in lying position	3.1-41.2	5.87	–
TSH [μIU/mL]	0.27-4.2	4.51	2.31
FT3 [pg/mL]	2-4.4	2.96	2.86
FT4 [ng/dL]	0.93-1.7	0.86	1.17
Parathormone [pg/mL]	15-65	39.2	31.1
25-hydroxyvitamin D [ng/mL]	30-50	9.8	12.1
Testosterone [ng/mL]	1.93-7.4	6.96	5.49
Prolactin [ng/mL]	4.04-15.2	14.1	8.5
IGF-1 [ng/mL]	57.4-187	89.3	126.8

ACTH — adrenocorticotropic hormone; DHEA — dehydroepiandrosterone; TSH — thyroid stimulating hormone; FT3 — triiodothyronine; FT4 — thyroxine; IGF-1 — insulin-like growth factor 1

Table 3. *Results of corticotropin-releasing hormone (CRH) test (100 μg i.v.)*

Time [min]	Patient 1		Patient 2	
	Cortisol [μg/dL]	ACTH [pg/mL]	Cortisol [μg/dL]	ACTH [pg/mL]
–15	2.2	19.6	0.4	3.9
0	2.4	19.3	0.4	3.6
15	1.9	18.4	0.6	8.0
30	2.1	19.8	0.9	8.0
60	1.9	21.7	0.7	5.2
90	2.0	20.6	0.5	3.2

ACTH — adrenocorticotropic hormone

and weak, with low blood pressure (90/60 mm Hg). At the beginning of diagnostics, normocytic anemia, hypoglycaemia, and hyponatremia with normal plasma potassium were diagnosed (Tab. 1). Mallory-Weiss' syndrome and duodenal ulcers were found in gastroscopy, and a benign polyp in colonoscopy. Abdominal CT revealed an incidentaloma of the left adrenal gland (4 HU, size: 20 × 30 × 14 mm). Additional diagnostics confirmed normal concentrations of methoxycatecholamines, aldosterone, and renin. A moderate cortical atrophy was noticed in MRI examination of the head. Bone marrow examination, chest CT scan, ECG, and heart ECHO were normal.

Based on hormonal results, low concentrations of morning cortisol and ACTH (Tab. 2), not increasing after CRH injection (Tab. 3), and normal concentrations of other pituitary hormones, IAD was diagnosed. Additionally, pituitary MRI was performed, excluding the presence of any abnormal lesions in the hypothalamic-pituitary region. Autoimmune disorders were excluded (antithyroid and anti-adrenal antibodies were negative). Antibodies against the pituitary autoantigens were not available at the time of the patient's hospitalization. Genetic analysis of the TBX19 gene was omitted due to the late onset of ACTH deficiency. Negative results of numerous imaging studies indicated a low probability of paraneoplastic autoimmune hypophysitis. The patient experienced a spectacular clinical improvement after introducing the replacement therapy with 20 mg of hydrocortisone *per os* (*p.o.*) (10 mg twice daily, 08.00 a.m., 02.00 p.m.), without any side effects. His weight and blood pressure normalized, and his sodium concentration reached 140 mmol/L (Fig. 1). After several weeks his anemia also improved.

Discussion

The presented cases with IAD show many similarities. Both patients were males over 60 years old, exemplifying that the disease begins after the age of 50 years with a slight male predominance [2]. They presented

similar symptoms typical for IAD, including fatigue, weakness, arterial hypotension, and weight loss [1, 2]. The results of basic laboratory tests with hyponatremia refractory to treatment, normokalaemia, and anemia were also comparable. Typically for IAD, an insidious and non-specific clinical presentation and laboratory results delayed the proper diagnosis [1, 2, 14].

We tried to establish the aetiology of IAD in our patients. Because many cases of acquired IAD are associated with autoimmune diseases, most frequently thyroid diseases [2, 7, 8], we excluded the thyroid and adrenal autoimmunity; however, pituitary antibodies were not available to us. Also, the pathogenic role of pituitary autoantibodies is unclear, and they are not specific for autoimmune pituitary diseases [17]. Positive pituitary antibodies were detected in the sera collected from patients with tumours of the hypothalamo-pituitary region [germinomas (33%), Rathke's cleft cysts (25%), craniopharyngiomas (17%), non-functioning pituitary tumors (13%), GH-secreting pituitary tumours (12%)] [17]. Moreover, autoimmune aetiology of IAD can be confirmed only in 70% cases, even with advanced immunological diagnostics [8].

Both our patients had a history of alcohol abuse. The first patient declared 2 years of abstinence, and all blood tests for ethanol were negative. At the beginning of observations, the history of drinking in the second patient was not so evident, but he also confessed to abusing alcohol. It was supported by the results of gastroscopy, in which the features of Mallory-Weiss' oesophagus, related to vomiting, typical for alcoholics, were confirmed.

The data on chronic alcohol abuse effects on the hypothalamic-pituitary-adrenal (HPA) axis are inconclusive [18]. In active drinkers, heavy alcohol consumption usually activates the HPA axis and leads to elevated cortisol levels [18, 19]. Excessive alcohol consumption is one of the causes of pseudo-Cushing syndrome, as confirmed by abnormal results of the 1 mg dexamethasone suppression test. On the other hand, in many studies carried out in chronic alcoholics inhibition of the HPA axis was demonstrated [20, 21]. The mechanism of such suppression is not clear, but a growing body of evidence indicates that alcohol abuse produces persistent dysregulation of several neurotransmitters and neuropeptides, including increased activity of gamma-aminobutyric acid (GABA), endogenous opiate (EOP), and atrial natriuretic peptide (ANP), which can inhibit the HPA axis [19]. In view of the medical literature, alcoholism may be a rare cause of IAD [13–15]. Kearney et al. [14] reported the history of 3 patients who chronically abused alcohol, diagnosed with IAD. All were over 40 years old, 2 of them were males, all presented confusion, anorexia, and one had low blood pressure. Severe hyponatremia without hyperkalaemia was found in all 3 of them, one had hypoglycaemia, and in 2 anemia was noted [14]. In other case reports [13, 15], severe hypoglycaemia was the main abnormality in the affected persons. It should be emphasized that all the aforesaid symptoms are common in alcoholics, which additionally impedes diagnostics. All patients were diagnosed with IAD based on low concentration of cortisol in the morning and additionally low ACTH and subnormal cortisol response in the short Synacthen test or insulin test, normal levels of other pituitary hormones, and the absence of structural lesions in the pituitary and hypothalamus [14].

Most of the presented patients experienced significant improvement after applying steroid therapy. However, it must be remembered that IAD is potentially life-threatening, and early diagnosis is closely related to patient prognosis. Two cases of death in IAD patients were reported [14, 22]; in one patient the direct reason of death was sepsis [14], in the another it was cardiorespiratory collapse [22].

Having excluded other causes of an IAD, such as autoimmune conditions (including paraneoplastic syndrome), abnormal MRI findings (tumour, injury, infectious, granulomatous diseases), surgery, and/or radiation therapy, as well as treatment with medicines affecting ACTH production, we hypothesize that the reason of IAD in our patients was related to long-term alcohol abuse. Non-characteristic clinical symptoms raise the possibility that cases of IAD with such an aetiology may be overlooked, especially in patients with chronic alcoholism. The stigma of alcohol addiction causes an additional delay in establishing the proper diagnosis.

Ethics

The study was approved by the Ethics Committee of the Polish Mother's Memorial Hospital - Research Institute (approval code no. 76/2021).

Conflict of interests

The authors declare that they have no competing interests.

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