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Diagnostic and therapeutic difficulties in a patient with corticotropic pituitary macroadenoma

Grzegorz Erbert[1], Elżbieta Łomna-Bogdanov[2], Marek Bolanowski[3]

[1]*Out-patient Endocrinology Clinic, Olesno, Poland*
[2]*Department of Endocrinology, Regional Hospital Opole, Poland*
[3]*Department of Endocrinology, Diabetes and Isotope Therapy, Medical University Wrocław, Poland*

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Cushing's disease is a rare endocrine disorder caused by a pituitary adenoma secreting adrenocorticotropic hormone (ACTH) resulting in excessive cortisol secretion by the adrenal glands and organ complications caused by hypercortisolaemia [1, 2]. Venous thromboembolism represents one of the most common complications of hypercortisolaemia [3, 4].

We present a clinical case of a patient diagnosed with ACTH-dependent Cushing`s syndrome in the course of corticotropic pituitary macroadenoma. Since 2000, the woman, M.K. (born 1969), complained of a gradual increase in body weight which was linked initially to stress and dietary habits. She had been suffering from hypertension and diabetes mellitus, both well controlled with medical therapy. Recurrent thrombophlebitis and ulcers of lower extremities were noteworthy. In addition, the patient reported muscle weakness and regular but scanty menses. She had a history of 3 pregnancies, natural childbirths, spinal pain syndrome with L5-S1 discopathy, and left wrist fracture. Physical examination revealed central obesity (body mass index [BMI] 49.0 kg/m^2) moon-shaped face, slight muscular atrophy of the iliac ring, acne, slight hirsutism – mainly on the upper lip and chin, and nail fungus. Typical symptoms such as facial plethora, purple striae, or excessive bruising were not observed. After another incident of thrombophlebitis complicated by thigh abscess, the patient was referred to the Endocrinology Department for hormonal diagnostics. Laboratory tests showed normal activated partial thromboplastin time (APTT) and D-dimer values, cortisol and ACTH levels in the diurnal profile were within the upper limit of normal, free cortisol excretion in the 24-hour urine sample was significantly elevated, but the 1 mg dexamethasone suppression test (DST) was negative (Tab. 1). Other tests showed hyperglycaemia, elevated glycated haemoglobin, and dyslipidaemia. Electrolytes (sodium, potassium, calcium, and phosphorus) were normal. Thyroid, parathyroid, and pituitary function were normal. At this time Cushing's syndrome was excluded. The patient was discharged home with the recommendation to intensify insulin therapy under the supervision of the diabetes clinic and hypotensive treatment.

A subsequent follow-up 2 years later showed elevated cortisol levels and a rigid diurnal profile, suppressed cortisol secretion following 2 mg/day DST for 48 h, ACTH levels rigid on the borderline of normal in the diurnal profile, and elevated cortisol excretion in the 24-hour urine sample (Tab. 2). MRI scan of the pitu-

Table 1. ***Laboratory results and diurnal profile of cortisol and adrenocorticotropic hormone (ACTH) secretion during the first hospitalisation (2014)***

Glucose [mg/dL]	216.0	N. 74–106	
Testosterone [ng/mL]	0.61	N. 0.08–0.48	
DHEA-S [μg/dL]	274.1	N. 60–337	
		Hour	
	8:00	17:00	24:00
Cortisol [μg/dL]	21.02	10.91	13.03
ACTH [pg/mL]	60.0	42.8	55.1
Prolactin [ng/mL]	24.45	32.05	46.41
Cortisol in the 24-hour urine [μg/24 h]	497; 879; 719		N. 50–190
Cortisol in 1-mg DST [μg/dL]	1.36		N. < 1.8

DHEA-S — dehydroepiandrosterone sulphate; ACTH — adrenocorticotropic hormone; DST — dexamethasone suppression test

Grzegorz Erbert MD, Out-patient Endocrinology Clinic, Jana Pieloka 14, 46-300 Olesno, Poland; e-mail: gerbert@o2.pl

Table 2. ***Laboratory results, diurnal profile of cortisol, and adrenocorticotropic hormone (ACTH) secretion and dexamethasone suppression test during the second hospitalisation (2015)***

Glucose [mg/dL]	145.0	N. 74–106	
DHEA-S [μg/dL]	294.9	N. 35–256	
	Hour		
	8:00	17:00	24:00
Cortisol [μg/dL]	23.48	18.29	21.64
ACTH [pg/mL]	39.4	30.5	50.8
Prolactin [ng/mL]	14.31	16.80	13.31
Cortisol in the 24-hour urine [μg/24 h]	230	N. 50–190	
Urinary cortisol in 2 mg/day DST for 48 h [μg/24 h]	97		
Urinary cortisol in 8 mg/day DST for 48 h [μg/24 h]	11		

DHEA-S — dehydroepiandrosterone sulphate; DST — dexamethasone suppression test

itary showed pituitary macroadenoma (12 × 15 × 7 mm size) protruding into the right sphenoid sinus (Fig. 1 and Fig. 2). The patient was qualified for transsphenoidal resection of the pituitary adenoma, which proved to be a non-radical procedure due to infiltration of the right sphenoid sinus and internal carotid artery (March 2016). The pathology report confirmed diagnosis of ACTH-secreting pituitary adenoma. Thereafter, ketoconazole was administered intermittently.

The next steps in the treatment were thermoablation of both adrenal glands and pituitary stereotactic radiotherapy using the CyberKnife technique (Dc-32 Gy in 4 fractions) performed in 2017. After the radiotherapy, an improvement in her general condition, and better diabetes and hypertension control were observed, as well as weight loss. Follow-up hormonal tests showed elevated ACTH, a rigid diurnal cortisol-ACTH profile, and normal daily urinary cortisol excretion.

After 3 years of remission, the disease progressed, exacerbating symptoms of venous thromboembolism with thrombosis of the right popliteal vein and ulceration of both lower extremities. The patient died in 2022 due to thromboembolic complications despite intensive antithrombotic treatment.

Comment: The diagnosis of Cushing's disease, despite its characteristic phenotype, can be very difficult. Differentiation of simple obesity from Cushing`s syndrome is sometimes problematic because patients with increased glucocorticosteroid receptor sensitivity present with a cushingoid phenotype of simple obesity in which there is increased cortisol production, dependent on body mass. Obese patients present with a normal diurnal rhythm of cortisol and ACTH secretion, serum cortisol levels, normal cortisol excretion in the 24-hour urine sample, and a normal (negative) 1 mg DST. In the case of doubt, and individual approach, long-term follow-up of patients, and regularly repeated endocrine diagnostics are always indicated [5].

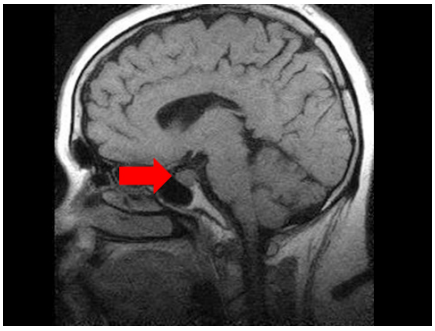

Figure 1. *Magnetic resonance (MR) image of the hypothalamo-pituitary system in a sagittal plane with visible pituitary tumour*

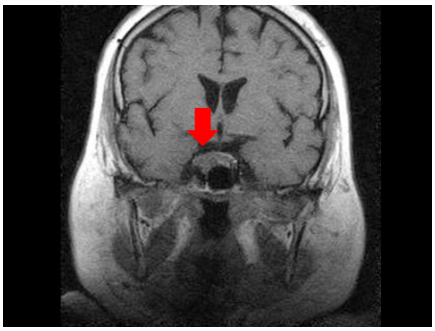

Figure 2. *Magnetic resonance (MR) image of the hypothalamo-pituitary system in a frontal plane with visible pituitary tumour*

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