Low Cortisol in a Cushingoid Patient

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CASE DESCRIPTION

A 52-year-old woman with a history of obesity and hypothyroidism saw her primary care provider (PCP), complaining of fatigue and a 30 pound (14 kg) weight gain over 3 months. Her body mass index was 45 kg/m2 and she had recently become hypertensive (blood pressure 136/83 mmHg). The PCP checked her early morning serum cortisol level and, surprisingly, it was low at 0.5 µg/dL (13.8 nmol/L) (reference interval [RI]: 4 to 225 µg/dL, 110 to 6208 nmol/L) (Table 1). Her hypothyroidism was well controlled on a stable dose of levothyroxine 50 µg daily. In light of the low morning cortisol level, she was referred to a community endocrinologist who noted her rounded facial appearance and redness on her cheeks. The patient reported facial hair growth, easy bruising, and striae on her legs. On repeated questioning, she denied any use of steroids. Repeat early morning serum cortisol on several occasions was 0.5 µg/dL (13.8 nmol/L) with suppressed plasma adrenocorticotropic hormone (ACTH) levels of <5 pg/mL (<1.1 pmol/L) (RI, 6 to 50 pg/mL, 1.32 to 11 pmol/L). Other serum pituitary hormone levels, as well as estradiol, dehydroepiandrosterone (DHEA) sulfate, and a comprehensive metabolic panel were all within the RIs.

Because of the low cortisol values, adrenal insufficiency was initially suspected and she was prescribed hydrocortisone 20 mg in the morning and 10 mg in the early afternoon. However, this caused increased anxiety, nervousness, and emotional lability. As reducing the hydrocortisone dose by 50% produced little improvement in these symptoms, the patient ultimately self-discontinued. Due to the discrepancy between her laboratory values and clinical presentation, she was referred to our medical center for further evaluation and management of her apparent adrenal insufficiency.

Approximately 3 months after stopping hydrocortisone, the patient's repeat serum cortisol and plasma ACTH levels by immunoassay remained low at 0.8 µg/dL (22 nmol/L) (RI, 8 to 25 µg/dL, 221 to 690 nmol/L) and 2 pg/mL (RI, 4 to 48), respectively. Given that the patient had a phenotype more consistent with hypercortisolism, these laboratory values were most unexpected. To exclude the possibility of interference with the serum cortisol immunoassay, liquid chromatography–tandem mass spectrometry (LC-MS/MS) was used to measure urine and salivary cortisol; her 24-h urine cortisol was <1.49 µg/g creatinine (<0.46 µmol/mol) (RI, < 24 µg/g, < 7.4 µmol/mol) and salivary cortisol was 0.015 µg/dL (0.41 nmol/L) (RI, 0.149 to 0.739 µg/dL, 4.11 to 20.39 nmol/L), confirming the low concentrations previously obtained using immunoassay. A comprehensive serum steroid panel by LC-MS/MS showed broad suppression of endogenous steroid synthesis with low 11-deoxycortisol, 17-hydroxyprogesterone, 17-hydroxypregnenolone, 18-hydroxycorticosterone, cortisol, cortisone, corticosterone, androstenedione, unconjugated DHEA, deoxycorticosterone, pregnenolone, progesterone, and testosterone levels.

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QUESTIONS TO CONSIDER
• What are the clinical features of Cushing syndrome and laboratory tests used to make the diagnosis?
• What are the causes of a decreased serum cortisol concentration?
• How does dexamethasone affect the hypothalamic–pituitary–adrenal axis?
• Can substances not mentioned in the product label be found in dietary supplements?

Table 1. Laboratory results (all specimens are serum, unless indicated).[a]

Test	Result	Reference interval
Cortisol, AM	0.7 μg/dL	4-22
ACTH, plasma	<5 pg/mL	6-50
Estradiol	<15 pg/mL	≤31
Dehydroepiandrosterone (DHEA) sulfate	5 ng/mL	8-188
Testosterone, total	4 ng/dL	2-45
Follicle-stimulating hormone	47.8 mIU/mL	23-116.3
Luteinizing hormone	32.1 mIU/mL	10-54.7
Insulin-like growth factor 1 (IGF-1)	119 ng/mL	50-317
IGF-1, z-score	−0.3	−2.0 to +2.0
Prolactin	10.4 ng/mL	2-20
Thyroid-stimulating hormone	3.25 mIU/L	0.40-4.50
Thyroxine, free	1.3 ng/dL	0.8-1.8
Aspartate transaminase	51 U/L	10-35
Alanine transaminase	80 U/L	6-29
Alkaline phosphatase	138 U/L	37-153
Bilirubin	0.6 mg/dL	0.2-1.2
Blood urea nitrogen	11 mg/dL	7-25
Creatinine	0.69 mg/dL	0.5-1.05
Glucose	89 mg/dL	65-99
CO_2	30 mmol/L	20-32
Sodium	142 mmol/L	135-146
Potassium	4.0 mmol/L	3.5-5.3
Chloride	103 mmol/L	98-110
Albumin	4.1 g/dL	3.6-5.1
Total protein	7.0 g/dL	6.1-8.1

[a]SI conversion factors: cortisol nmol/L x 27.6; estradiol pmol/L x 3.67; DHEA sulfate nmol/L x 3.47; testosterone pmol/L x 34.7; bilirubin umol/L x 17.1; blood urea nitrogen mmol/L x 0.357; creatinine umol/L x 88.4 ; glucose mmol/L x 0.055.

Final Publication and Comments

The final published version with discussion and comments from the experts will appear in the June 2023 issue of *Clinical Chemistry*. To view the case and comments online, go to https://academic.oup.com/clinchem/issue/69/6 and follow the link to the Clinical Case Study and Commentaries.

Educational Centers

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