

Glucocorticoid Hypersensitivity Syndrome – A Case Report

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ABSTRACT

Glucocorticoid hypersensitivity syndrome has been reported to date only in several patients. This article describes a unique case of this syndrome in a 24-year old female admitted to hospital because of arterial hypertension and obesity. Although her clinical picture suggested Cushing's syndrome, she had low adrenocorticotrophic hormone (ACTH) and cortisol levels with a poor response to corticotrophin-releasing hormone and Synacthen. In turn, an overnight dexamethasone suppression test with 0.25 mg of dexamethasone led to a dramatic decrease in morning cortisol. A diagnosis of glucocorticoid hypersensitivity was made and the patient started treatment with ketoconazole and cabergoline, which resulted in some clinical improvement. This case illustrates the need for clinical awareness of glucocorticoid hypersensitivity in patients suspected of Cushing's syndrome.

Keywords: Adrenal cortex function, Cushing's syndrome, diagnosis and treatment, receptor hypersensitivity

Síndrome de la Hipersensibilidad Glucocorticoidea Reporte de Caso

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RESUMEN

El síndrome de la hipersensibilidad glucocorticoidea ha sido reportado hasta la fecha en varios pacientes. Este artículo describe un caso único de este síndrome en una mujer de 24 años, ingresada en el hospital debido a hipertensión arterial y obesidad. Aunque su cuadro clínico hizo pensar en el síndrome de Cushing, presentaba un bajo nivel tanto de hormona adrenocorticotropa (ACTH) como de cortisol, acompañado de una respuesta pobre a la hormona liberadora de corticotropina y al synacthen. A su vez, una prueba de supresión de la dexametasona realizada durante la noche con 0.25 mg de dexametasona, condujo a una disminución dramática del cortisol en la mañana. Se hizo un diagnóstico de hipersensibilidad glucocorticoidea, y la paciente empezó el tratamiento con ketoconazol y cabergolina, lo cual trajo como consecuencia cierta mejoría clínica. Este caso ilustra la necesidad de una mayor conciencia clínica en torno a la hipersensibilidad glucocorticoidea en pacientes sospechosos de padecer el síndrome de Cushing.

Palabras claves: Función de la corteza suprarrenal, síndrome de Cushing, diagnóstico y tratamiento, hipersensibilidad, receptor

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INTRODUCTION

Only few cases of glucocorticoid hypersensitivity syndrome have been reported in the literature to date. Patients diagnosed with this clinical entity are characterized by the presence of the clinical manifestations of Cushing's syndrome, despite normal or even low levels of endogenous

glucocorticoids (1–4). This hypersensitivity is either generalized or is more expressed in peripheral tissues than in the hypothalamus and pituitary (2). Apart from excluding iatrogenic Cushing's syndrome, the diagnosis of glucocorticoid hypersensitivity syndrome always requires ruling out the presence of clinical conditions associated with a decreased production and/or enhanced metabolism of corticosteroid-binding globulin (CBG), in which despite low total cortisol levels, the concentration of its free fraction remains within normal limits and therefore affected patients usually do not present with clinical symptoms of abnormal function of the adrenal cortex (5).

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In the present paper, we report a young woman with glucocorticoid hypersensitivity who developed the clinical picture of Cushing's syndrome despite low plasma cortisol levels. We describe diagnostic and treatment strategies utilized in this patient.

CASE REPORT

A 28-year old woman was hospitalized because of arterial hypertension and prediabetes. Although arterial hypertension had been treated with amlodipine, bisoprolol and enalapril, her blood pressure control was not satisfactory. The patient did not receive any other drugs. Over the last two years, the patient's body weight increased by 24 kg. On admission, both her body weight (92 kg, body mass index – 35.2 kg/m²) and blood pressure (170/110 mmHg) were increased. Physical examination revealed central obesity with cervical buffalo hump, a rounded face, facial plethora, a dorsal fat pad, supraclavicular fullness, thin skin with bruises and proximal myopathy. Abdominal obesity contrasted with thin extremities and she had thick, purple striae on the abdomen. Plasma cortisol levels were 5.3 µg/dL (reference range: 8.0–25.0 µg/dL) in the morning and 3.2 µg/dL at midnight. Both the morning and midnight plasma adrenocorticotropic hormone (ACTH) levels were undetectable (< 5 pg/mL, reference values: 10–80 pg/mL). Twenty-four hour urinary free cortisol excretion, on two independent samples, was 12 and 14 µg/day (reference values: 20–90 µg/day). Plasma dehydroepiandrosterone sulfate levels were decreased (52 µg/dL; reference values: 80–450 µg/dL). Both midnight plasma cortisol and late-night salivary cortisol were very low (1.2 µg/dL, reference values below 7.5 µg/dL; 0.04 µg/dL and below 0.27 µg/dL, respectively). Neither ACTH nor cortisol plasma levels significantly increased after corticotropin-releasing hormone stimulation. A 250 µg cosyntropin stimulation test showed a poor cortisol response with a peak cortisol level of 4.8 µg/dL (reference values >19.6 µg/dL). An overnight dexamethasone suppression test (single dose of 1 mg of dexamethasone) resulted in a dramatic decrease in morning cortisol levels to 0.05 µg/dL. Corticosteroid-binding globulin levels (41 mg/L) were within normal limits (35–50 mg/L). Urinary catecholamines, metanephrines and normetanephrines were normal, and tests for primary aldosteronism were negative. Bone density of lumbar vertebrae assessed by dual-energy X-ray absorptiometry revealed the presence of osteoporosis (Z-score – 3.5). An abdominal computed tomography scan revealed small adrenal glands. A pituitary magnetic resonance imaging (MRI) did not reveal any abnormalities in the *sella turcica*. We excluded thyroid dysfunction (normal levels of thyroid stimulating hormone and free thyroid hormones), polycystic ovary syndrome (normal levels of testosterone, androstenedione, normal free androgen index, lack of clinical manifestations of androgen excess and of typical ultrasonographic features in the ovaries) and congenital adrenal hyperplasia

(17-hydroxy-progesterone at baseline was within the reference range). Because this clinical picture suggested glucocorticoid hypersensitivity, a dexamethasone suppression test with a very low dose (0.25 mg) of dexamethasone was performed and showed a marked decrease in plasma cortisol to 0.1 µg/dL, which was consistent with the diagnosis of glucocorticoid hypersensitivity (2, 4). Although the drug of choice in treatment of glucocorticoid hypersensitivity is mifepristone, this agent is not available in Poland. Instead, we decided to further reduce cortisol secretion by administration of ketoconazole at the daily dose of 400 mg. Because four-month ketoconazole treatment, apart from preventing further weight gain, produced no clinical benefits, cabergoline (1 mg weekly) was added to ketoconazole. Following the cabergoline-ketoconazole combination, the patient's clinical condition improved. Her blood pressure, although still increased, was effectively controlled by bisoprolol and amlodipine treatment, while values of fasting and post-challenge plasma glucose levels were within normal limits. Although body weight fell by 11 kg, clinical features of Cushing's syndrome were, however, still present. Unfortunately, after eight years of treatment with cabergoline and ketoconazole, the patient died in a road traffic accident.

DISCUSSION

The report describes a very rare case where typical clinical manifestation of Cushing's syndrome coexisted with low plasma levels of cortisol and ACTH. These results as well as a poor response of ACTH and cortisol to corticotropin-releasing hormone stimulation and cortisol to Synacthen stimulation indicate that the hypothalamic-pituitary-adrenal axis in the patient was suppressed at all levels. Interestingly, the subject was characterized by a robust inhibitory response of the adrenal glands to dexamethasone, observed even when this agent was administered at a very low dose, which is insufficient to reduce cortisol secretion to such a degree in both healthy subjects and patients with Cushing's syndrome (1). Although we did not assess the response of peripheral blood mononuclear cells to dexamethasone (6), it seems that both the clinical picture and the results of hormonal analysis were enough to establish the diagnosis of glucocorticoid hypersensitivity. Normal values of plasma renin activity, plasma aldosterone levels and aldosterone-to-renin ratio indicate that hypersensitivity in this patient was limited to the glucocorticoid receptor.

It is assumed that the best treatment for subjects with glucocorticoid hypersensitivity is glucocorticoid receptor antagonists, particularly mifepristone, which blocks both the progesterone and glucocorticoid receptors and weakens the potency of glucocorticoid receptor action, and this effect is paralleled by an increase in cortisol and ACTH plasma levels (7, 8). Because of the lack of availability, instead of glucocorticoid receptor antagonists, we decided to further reduce plasma cortisol levels. Some clinical improvement was

noted only after the combined administration of ketoconazole and cabergoline. Both these agents affect the hypothalamic-pituitary-adrenal axis activity at different levels. Ketoconazole is an inhibitor of adrenal steroidogenesis while cabergoline inhibits pituitary ACTH secretion (9, 10). What is worth mentioning is that this combination treatment was well tolerated and did not result in the development of adrenal insufficiency during a seven-year follow-up period.

In conclusion, this case illustrates the need for clinical awareness of glucocorticoid hypersensitivity in patients suspected of Cushing's syndrome in whom the hypothalamic-pituitary-adrenal axis activity is suppressed. Although glucocorticoid receptor antagonists seem to be the drug of choice in the management of this clinical entity, some benefits may be obtained by the combination treatment of cabergoline and ketoconazole in glucocorticoid hypersensitivity patients.

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