 DOI: 10.18231/2348-7240.2017.0010

Glucocorticoid hypersensitivity syndrome: a rare case report

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Abstract

Glucocorticoid hypersensitivity syndrome (GHS) is a rare clinical entity. It is characterised by clinical features of Cushing syndrome with normal or sometimes low levels of ACTH and cortisol, with poor response to corticotrophin releasing factor (CRH) and synacthen. We report a case of 18 years old female who presented with obesity and hypertension. A diagnosis of GHS was made and the patient was managed with ketoconazole and cabergoline.

Keywords: Cushing's syndrome, Glucocorticoid hypersensitivity syndrome (GHS)

Introduction

Glucocorticoid hypersensitivity syndrome (GHS) is characterised by clinical manifestations of Cushing's syndrome inspite of normal to low levels of endogenous glucocorticoids.[1,2] This hypersensitivity maybe generalized or present in peripheral tissues rather than in hypothalamus or pituitary.[3] The diagnosis of GHS is made on decreased production or increased metabolism of corticosteroid binding globulin (CBG) so that the patients manifest symptoms of abnormal functioning of adrenal cortex.[4]

Case Report

An 18 years old girl presented with increase in body weight and hypertension. She was taking two antihypertensive medications- enalapril and cilnidipine but her blood pressure (BP) was poorly controlled. She had gained 12 Kgs of weight over the last one year. She was non-diabetic and her menstrual cycles were normal. Her body weight was 90 Kgs, body mass index (BMI) was 34.8 Kg/ m^2, and BP was 180/100 mm Hg. Physical examination revealed central obesity, buffalo hump at the back, rounded face, facial plethora, supraclavicular fullness, thin skin with bruises and proximal myopathy. Her abdomen examination revealed presence of thin purple striae. Laboratory investigations revealed that her haemoglobin, total leucocyte count, differential leucocyte count, blood urea, serum creatinine, fasting blood sugar levels were within normal limits. Lipid profile revealed serum cholesterol 215 mg/dl, triglycerides 280 mg/dl, low density lipoprotein 140 mg/dl, high density lipoprotein 30 mg/dl. Plasma cortisol levels were 6.2 micrograms/dl. The normal reference range for morning cortisol is 7-25 micrograms/dl.[5] The midnight cortisol levels in this patient were 1.24 micrograms/ dl. Studies have suggested that awake midnight serum cortisol level >7.5 micrograms/dl is diagnostic of Cushing's syndrome.[6,7] In our patient 24 hour urinary free cortisol excretion on two independent samples was 10 and 12 micrograms/ day. The normal range for urinary free cortisol excretion is between 3.5-45 micrograms per day.[8] Plasma dehydroepiandrosterone (DHEA) level was 40 micrograms/dl (Normal range 145-395).[9] Late night salivary cortisol was 30 nanograms/dl (normal <100 nanograms/ dl).[10] CRH stimulation did not increase ACTH and plasma cortisol levels. With 25 micrograms cosyntropin stimulation test, plasma cortisol was 4.6 micrograms/ dl (Reference value >20 micrograms/dl).[11] An overnight dexamethasone suppression test resulted in significant fall in morning cortisol levels to 0.04 micrograms/dl (normal range 3-6-7.2 micrograms /dl).[12] Corticosteroid binding globulin levels were 39 mg/L (Normal range 38-50).[13] Tests for primary aldosteronism were negative. Urinary catecholamines, metanephrines and nor metanephrines were normal. CT abdomen revealed small adrenal glands. MRI of pituitary did not show abnormalities in sella tursica. Thyroid function tests and prolactin levels were normal. Tests for polycystic ovary syndrome and congenital adrenal hyperplasia were normal. Clinical diagnosis of GHS was made. For this a very low dose (0.25 mg) of dexamethasone suppression test was done which showed a marked decrease in plasma cortisol to a level of 0.1 micrograms/ dl, which was diagnostic of glucocorticoid hypersensitivity.[1,3] The patient was put on 400 mg of daily dose of ketoconazole for 3 months but with little benefit. So we added 1 mg weekly dose of cabergoline with ketoconazole. The patient responded dramatically with control of blood pressure and weight.

Discussion

Our patient had typical clinical features of Cushing's syndrome along with low levels of cortisol and ACTH. Demonstration of poor response of ACTH and cortisol to corticotrophin releasing hormone stimulation, as well as cortisol to synacthen stimulation showed suppression of hypothalamic-pitutary-adrenal axis. In this patient glucocorticoid receptor

hypersensitivity was reflected by normal levels of plasma rennin activity, plasma aldosterone levels, and aldosterone to rennin ratio. The treatment of choice for such patients is mifepristone, which is a glucosteroid receptor antagonist, and is known to increase cortisol and ACTH levels.[14] As mifepristone is very costly, our patient was not prescribed this medication because of her inability to afford it. Instead the treatment was continued with ketoconazole. To further decrease plasma cortisol levels, cabergoline was added to ketoconazole regime. Both these agents affect the hypothalamic-pitutary-adrenal axis actively at different levels. Ketoconazole inhibits steroidogenesis, while cabergoline inhibits ACTH secretion.[15,16]

Conclusion

GHS should be suspected in those patients of Cuching's syndrome who has suppression of the hypothalamic-pitutary-adrenal axis. Cabergoline in combination with ketoconazole shows better response in GHS rather than ketoconazole given alone.

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