case report

A case of hypocortisolemic clinical Cushing's syndrome

Kamal A.S. Al-Shoumer, Mohamad F. Hafez, Suhail A.R. Doi

From the Division of Endocrinology, Faculty of Medicine, Kuwait University and Mubarak Al-Kabeer Hospital, Kuwait

Correspondence and reprints: Associate Professor Kamal A.S. Al-Shoumer · Division of Endocrinology, Faculty of Medicine, Kuwait University · PO Box 24923, Safat 13110, Kuwait · T: +965 5319596 · kshoumer@gmail.com · Accepted for publication May 2007

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The symptoms and signs of Cushing's syndrome result directly from chronic exposure to excess glucocorticoids. Most actions of glucocorticoids are mediated by the glucocorticoid receptor. Several polymorphisms in the gene coding for the glucocorticoid receptor have been described and these may contribute considerably to the observed variability in glucocorticoid sensitivity.[1] At the tissue level, the enzyme 11β-hydroxysteroid dehydrogenase type I modulates the effect of glucocorticoids. Both animal and human studies have demonstrated that alterations in 11β-hydroxysteroid dehydrogenase type I activity in adipose tissue and liver are associated with the metabolic syndrome, thus possibly reflecting a tissue-specific (omental) Cushing's syndrome.[2]. Cellular hyperreactivity to glucocorticoids at the mRNA level has also been demonstrated.[3] It is not surprising, therefore, that cases of Cushing's syndrome with putative receptor dysfunction exist, and we report one such likely case and review the literature on this topic.

CASE

A 32-year-old female was referred to our department in August 2000 for evaluation of cushingoid features. She gave a history of recurrent abdominal pain and renal stones from 1987 to1993. Hypertension and diabetes mellitus were diagnosed in 1994 and she had since been on treatment with lisinopril and insulin. In 1995, her treating doctor observed that she had clinical features of Cushing's syndrome. Evaluation of her condition then revealed very low serum cortisol levels without diurnal variation and undetectable 24-hour urinary cortisol. CT of her adrenals demonstrated a picture suggestive of left supra-renal myelolipoma while MRI of the pituitary was normal. In November 1995, she went to a private practice where she underwent left adrenalectomy (with unavailable histopathology report) and was replaced with glucocorticoids for one year for a short period of time. Thereafter she received no glucocorticoids or other steroid-containing drugs. Occasionally she complained of difficulty in standing from a sitting or lying position without aid. She had normal and regular menses.

On examination she was conscious, oriented, and her blood pressure was moderately high (150/110 mm Hg) with a regular and normal pulse rate. She had a round plethoric face with an increased amount of supraclavicular fat. She was centrally obese with thin extremities and her skin was thin with purple striae on the abdomen. She had proximal muscle weakness in the lower limbs. Axillary and pubic hairs were present and she was not hirsute. The thyroid was not enlarged. The rest of her examination was unremarkable. Her work-up demonstrated undetectable cortisol in a 24-hour urine (repeated twice). The morning cortisol at 8 AM was low at 28 nmol/L (repeated twice) and the morning adrenocorticotropic hormone (ACTH) at 8 AM was low at <10 pg /mL (normal range, 10-46 pg /mL). There was a very poor cortisol response to the synacthen (ACTH [1-24]) 250 μg stimulation test (0 min: 14.9 nmol/L; 30 min: 42.4 nmol/L; 60min: 67.5 nmol/L). No ACTH or cortisol response to corticotrophin releasing hormone (CRH) stimulation was seen and all samples had ACTH <10.0 pg/mL and cortisol <13.8 nmol/L. Urine analysis for 17-ketosteroids by gas chromatography-mass spectrometry revealed total 17-ketosteroids of 17.33 μmol/24h (normal range, 11.50-38.00 μmol/24h), androsterone 7.24 μmol/24h (normal range, 3.50-9.30 μmol/24h) and dehydroepiandrosterone of 1.06 μmol/24h (normal range, 1.20-4.60 μmol/24h). She had normal thyroid function (free T3 5.4 pmol/L, free T4 22.7 pmol/L, sensitive TSH 3.6 mU/L). Her luteinizing hormone (LH) was 33.9 IU/L (normal range, 2.4-16.7 IU/L), follicle-stimulating hormone was 16.6 IU/L (normal range, 2.1-9.0 IU/L), and estradiol was 808 pmol/L (normal range, 35-285 pmol/L). She was hyperandrogenic with a total testosterone of 3.2 nmol/L (normal range, 0.3-3.0 nmol/L), sex-hormone binding globulin of 27 nmol/L (normal range, 20-118 nmol/L) and free androgen

index of 11.9% (normal range for females, <4.5%). Dihydroepiandrosterone sulfate was suppressed at 0.6 μmol/L (normal range, 0.9-11.7 μmol/L), but 17-hydroxyprogesterone was normal at 4.1 nmol/L (normal range, 0.3-14.5 nmol/L) while androstenedione was low at 1.9 nmol/L (normal range, 1.6-9.4 nmol/L). Fasting plasma glucose was elevated at 7.3 mmol/L. The complete blood count was normal and there was no liver dysfunction or renal impairment. Serum electrolytes and mineral profile were normal. Total cholesterol was high at 7.05 mmol/L, but triglycerides were normal 0.59 mmol/L and high-density lipoprotein was 2.30 mmol/L. During follow up, she was taking either lisinopril or amlodipine in addition to insulin and there was no change in her clinical condition, biochemical profile or in repeated cortisol measurements in the urine or serum.

DISCUSSION

The glucocorticoid receptor is a ligand-dependent transcriptional regulator that mediates a panoply of developmental, physiological, and behavioral processes.[4] The glucocorticoid receptor is not the sole determinant of the cellular response to ligands; other cellular factors are known to modulate glucocorticoid receptor action. For example, hormone transporters,[5,6] molecular chaperones,[7] chromatin remodeling factors,[8,9] coactivators,[10] as well as other transcription factors such as AP-1[11] interact with the glucocorticoid receptor and affect its function. Mutations of the glucocorticoid receptor result in syndromes of local and generalized glucocorticoid resistance, glucocorticoid hypersensitivity, hypercortisolism, and increased cortisol response to stress.[12] Whereas decreased sensitivity to the corticosteroid receptor is described more frequently, Iida and colleagues first described increased sensitivity to the glucocorticoid receptor in 1990[13] in a patient that had clinical characteristics of Cushing's syndrome and low cortisol concentrations on several occasions. Exogenous corticosteroids were the best explanation for the clinical picture and laboratory abnormalities, but this could not be confirmed and the patient's history lacked any information. Other possibilities that should have been considered include intermittent Cushing's syndrome, promiscuous receptor-induced Cushing's syndrome and silent pituitary infarction of ACTH-producing adenoma. Intermittent Cushing's was excluded by the lack of raised cortisol levels (urine and serum) on repeated measurements at different intervals, whereas promiscuous receptor-induced Cushing's could not be confirmed. Silent pituitary infarction was also excluded by the normal level of anterior lobe pituitary hormones and by the normal pituitary gland by MRI. The authors therefore considered a cortisol hyperreactive syndrome as a plausible possibility in this patient. In vitro experiments with the patient's skin fibroblasts supported the concept of an increased sensitivity to glucocorticoids. More recently, Huizenga and colleagues[14] described a polymorphism in the glucocorticoid receptor that was associated with increased receptor sensitivity. In that study, 13 patients carrying a mutation in the glucocorticoid receptor (N363S carriers) were identified. The patients with this mutation had a significantly higher body mass index (BMI) and there was a trend towards a lower bone mineral density, which suggests that they were more sensitive to the effects of glucocorticoids. A low-dose dexamethasone suppression test, using 0.25 mg instead of 1 mg dexamethasone, demonstrated significantly larger cortisol suppression in the N363S carriers.[14] Another case has been described by Newfield and colleagues of cushingoid features in prepuberty in the presence of normal cortisol levels. This patient was subsequently reported to have markedly elevated glucocorticoid receptor sites per peripheral lymphocyte with normal binding affinity as a potential cause of her phenotype.[15]

In another report, a patient who received two intra-articular triamcinolone acetonide injections developed the clinical characteristics of Cushing's syndrome and had asymptomatic adrenal insufficiency, which resolved after 6 months. Therefore, increased sensitivity may also be subclinical and manifest after exposure to exogenous glucocorticoids. In this patient, a dexamethasone suppression test, using 0.25 mg instead of 1 mg dexamethasone, demonstrated a significant decrease in the morning cortisol. The response of peripheral blood mononuclear cells to dexamethasone in a mitogen-stimulated proliferation assay in this patient showed a lower IC50 than normal controls, supporting the diagnosis of increased glucocorticoid sensitivity.[16] Hyperreactivity of our patient to glucocorticoids, either at the receptor or at the post-receptor level could explain her cushingoid features if she had ingested even very small amounts of glucocorticoids. However, her hypocortisolemia predates her adrenal surgery and glucocorticoid use suggesting that she had overt activation of the glucocorticoid receptor (or post-receptor mechanisms).

The diagnosis of hypocortisolemic Cushing's syndrome is based on clinical suspicion, followed by documentation that low cortisol levels are not associated with steroid intake. In our patient we documented a low cortisol level, a flat response to ACTH stimulation, no response to the CRH stimulation test and after a

careful history, observation and intensive investigation, we excluded any possible steroid intake. In Cushing's disease, the chronic hypercortisolemia inhibits hypothalamic CRH secretion and also inhibits ACTH secretion by the normal, nonadenomatous pituitary corticotrophs, which atrophy. The concentrations of CRH in the cerebrospinal fluid, and presumably in the hypophysial-portal circulation, are reduced.[17] Also, exogenous glucocorticoids inhibit CRH and ACTH secretion, causing bilateral adrenocortical atrophy. Plasma ACTH, serum and salivary cortisol concentrations, and urinary 17-hydroxycorticosteroids and cortisol excretion (unless cortisol is the steroid administered) are all low.[18] We suggest that in patients with wild-type receptors, minimal amounts of glucocorticoids will suppress the hypothalamic-pituitary-adrenal axis effectively. Although not reported before, we thought about the effect of lisinopril on aberrant receptors, but substituting it with amlodipine resulted in no improvement in her clinical condition or her biochemical profile.

The possible approach to treatment of these patients is the use of the progesterone and glucocorticoid receptor antagonist RU-486 (mifepristone), which is a potent antagonist of both of these receptors. It is the only drug administered to humans with these actions.[19] In normal subjects, it inhibits dexamethasone suppression and raises endogenous cortisol and ACTH values.[20] To date, RU-486 has been used in a handful of patients with Cushing's syndrome. In a placebo-controlled trial of the acute effects in seven patients given 200 mg orally every 12 hours, plasma and urinary glucocorticoids were raised in five patients with Cushing's disease after 2 days.[21] Other reports describe treatment of a few patients, with symptomatic improvement at doses of 5-20 mg/kg/day.[22-25] Prompt reversal of neuropsychiatric symptoms has been reported in two cases of hypercortisolemic psychosis.[24] However long-term data are unavailable as the longest period of treatment reported was 10 weeks.[22] The main drawback with use of this agent is the induction of an iatrogenic cortisol deficiency state, but Addisonian crisis responds to a dose reduction. Because of its novel site of action, with receptor antagonism leading to increased cortisol and ACTH levels, the diagnosis of treatment-induced glucocorticoid insufficiency rests on clinical grounds. Limited clinical experience with RU-486 in Cushing's syndrome suggests that it is highly effective in reversing the manifestations of hypercortisolism, but it is not known if the same will hold true for glucocorticoid hypersensitivity. While RU-486 has been effective in small numbers of patients treated for relatively short periods of time, the long-term efficacy and side effects of glucocorticoid and progesterone receptor blockade remain to be determined.

The inter-individual response to glucocorticoids varies considerably; thereby diagnosis of Cushing's syndrome should be based on clinical suspicion. In certain circumstances, an absence of hypercortisolemia should not exclude the diagnosis of Cushing's, as other factors at cellular levels can determine the individual response to cortisol. To date, most of these factors are still under investigation. Full knowledge of these factors may result in new diagnostic criteria for Cushing's with a potential for new pharmacological therapies.

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