Prolonged Adrenal Suppression after Adrenalectomy for Subclinical Hypercortisolism

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KEY WORDS: adrenal mass, subclinical Cushing syndrome, prolonged adrenal suppression, glucocorticoid receptor genes, glucocorticoid replacement

SUBCLINICAL CUSHING SYNDROME

Subclinical Cushing syndrome (SCS) is defined as a subtle cortisol overproduction in patients without the typical signs and symptoms of hypercortisolism. The growing interest in this entity is mainly due to extensive evaluation of incidentally discovered adrenal masses in order to exclude autonomous hormonal hypersecretion [1]. The management of subclinical hypercortisolism is challenging because of the lack of clear diagnostic parameters and the prevalence of obesity and other components of metabolic syndrome in the general population [1,2]. Variability in glucocorticoid sensitivity due to polymorphisms of glucocorticoid receptor genes and the difference in individual hypothalamo-pituitary sensitivity to cortisol may also play a role in the presence of mild hypercortisolism [3].

PATIENT DESCRIPTION

A 45 year old woman was referred for right adrenal mass discovered on a computed tomography (CT) scan during evaluation for hypertension. She had a 6 year history of poorly controlled hypertension, early menopause and depressive disorder. On examination, blood pressure was 150/90 mmHg, weight 88 kg, height 175 cm, and body mass index 28 kg/m². There was no dorsocervical fat pad, enlargement of abdo-

men, skin changes, hirsutism, plethora, or muscle weakness. She underwent a comprehensive evaluation of hypertension. Measurements of 24 hour urinary free cortisol on three occasions were 255, 196 and 305 nmol/24 hour (normal ≤ 208), with appropriate volume. The overnight 1 mg dexamethasone suppression test revealed lack of cortisol suppression (cortisol 13.9 µg/dl), inappropriately increased midnight cortisol level (13 µg/dl), suppressed ACTH (< 5 pg/ml), and normal DHEAS level of 76 µg/dl (35–430 µg/dl). Due to a high plasma aldosterone/renin ratio, an intravenous saline loading test was performed, which excluded hyperaldosteronism. Abdominal CT revealed a 3.5 cm hypodense mass with regular border in her right adrenal. No contrast washout was obtained, but pre-contrast Hounsfield unit (HU) measurement was 13. The diagnosis of subclinical Cushing’s syndrome was made.

After discussing the options for further treatment with the patient, a laparoscopic adrenalectomy was performed. The resected mass was a well-circumscribed golden yellow nodule measuring 3.5 x 3 x 2 cm. The histopathology specimen confirmed a cortical adenoma.

One week postoperatively she started feeling unwell with increasing weakness, loss of stamina, and more depressive mood. Adrenal insufficiency was diagnosed and she started on a replacement dose of cortisol acetate. The full recovery of adrenal function occurred 1½ years after adrenalectomy. The chronology of the ACTH stimulation test is shown in Table 1.

Following surgery, a marked improvement in hypertension was noted. The patient was treated with only one antihypertensive drug, leading to excellent blood pressure control. The blood pressure measurement on her last visit was 106/78 mmHg. After surgery, she intentionally changed her life habits. She has lost 12 kg of weight with diet and her last BMI was 25 kg/m². She quit smoking and her metabolic profile 6 months after surgery showed a noticeable improvement. Her triglyceride level declined from 243 to 73 mg/dl, and total cholesterol from 175 to 148 mg/dl. Her high density lipoprotein remains unchanged after the surgery (61 mg/dl), and blood glucose was in the normal range before and after surgery. She has an exacerbation of her depression, which is treated with selective serotonin reuptake inhibitor (SSRI). Serial low dose (1 µg) ACTH stimulation tests are performed to assess recovery of the hypothalamo-hypophysis-adrenal axis.

COMMENT

Subclinical Cushing’s syndrome (SCS) is a subtle cortisol hypersecretion that causes hypothalamic-pituitary-adrenal (HPA) axis dysfunction without the typical stig-

Table 1. Chronology of ACTH tests

<table>
<thead>
<tr>
<th>Cortisol (µg/dl)</th>
<th>23 April 2014</th>
<th>2 July 2014</th>
<th>6 November 2014</th>
<th>22 January 2015</th>
<th>10 October 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>&lt; 1</td>
<td>&lt; 1</td>
<td>1.49</td>
<td>5.8</td>
<td>12</td>
</tr>
<tr>
<td>30 min</td>
<td>1.23</td>
<td>&lt; 1</td>
<td>3.58</td>
<td>9.1</td>
<td>16.3</td>
</tr>
<tr>
<td>60 min</td>
<td>-</td>
<td>&lt; 1</td>
<td>4.57</td>
<td>11.2</td>
<td>17.9</td>
</tr>
</tbody>
</table>
mata of Cushing’s syndrome. It is frequent in patients with adrenal incidentalomas and found in up to 20% of cases [1]. SCS is probably not an early stage of Cushing’s syndrome because development of full-blown Cushing’s rarely occurs in patients with adrenal adenoma and mild hypercortisolism [4]. The latter can be associated with high systemic levels of cortisol or with local hypercortisolism due to increased activity of 11ß-hydroxysteroid dehydrogenase 1 or genetic variations in glucocorticoid receptor gene [3]. Thus, individual variations in all components of the glucocorticoid system, including ligands, receptors and genes can play a role in glucocorticoid sensitivity and response of the entire axis [3].

Diagnostic criteria of SCS are based solely on laboratory tests. No clear consensus on biochemical workup of subclinical hypercortisolism has been reached. It seems that high midnight serum cortisol may be an early marker of cortisol excess [1] and two or more positive tests including 1 mg dexamethasone suppression test, urinary free cortisol, low ACTH, elevated midnight salivary cortisol or serum cortisol have the highest predictive value in the diagnosis of SCS [4].

The relationship of metabolic complications to subtle hypercortisolism status remains unclear. Increased prevalence of diabetes mellitus type 2, dyslipidemia, obesity and osteoporosis was found in patients with adrenal incidentaloma without cortisol hypersecretion. Improvement of metabolic profile and hypertension after surgery was noted in patients with or without SCS [1]. An increased prevalence of metabolic syndrome was found in the general population and therefore cannot be attributed to hypercortisolism. Taken together, the optimal treatment of SCS is not yet defined and remains a challenge. Probably most patients should be observed conservatively and operative treatment should be reserved for young patients with poorly controlled metabolic complications [1, 4].

Adrenal insufficiency (AI) after unilateral adrenalectomy occurs in about half the patients with subclinical hypercortisolism and can also arise in patients with completely normal preoperative hypothalamic-pituitary-adrenal (HPA) axis function. In the study by Eller-Vainicher et al. [5], higher midnight serum cortisol was the only reliable marker for prediction of subsequent adrenal insufficiency. Although the prevalence of adrenal insufficiency and the time to recovery are tightly related to the degree of hypercortisolism, severe and prolonged adrenal suppression may occur in patients with only subtle hypercortisolism at presentation [2].

Therefore, glucocorticoid replacement therapy should be recommended to all patients with adrenal incidentaloma undergoing adrenalectomy whether they have SCS or not. The replacement therapy may be safely stopped only after normalization of ACTH-stimulated cortisol levels.

In conclusion, prolonged adrenal suppression and need for glucocorticoid treatment for extensive periods should be taken into consideration and discussed with patients undergoing adrenalectomy. Changing lifestyle habits together with surgery can lead to marked improvements in metabolic syndrome attributable to adrenal incidentaloma.

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**References**


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**Capsule**

**Oxidative stress inhibits distant metastasis by human melanoma cells**

Solid cancer cells commonly enter the blood and disseminate systemically, but are highly inefficient at forming distant metastases for poorly understood reasons. Piskounova et al. studied human melanomas that differed in their metastasis histories in patients and in their capacity to metastasize in NOD-SCID-IL2R-/- (NSG) mice. The authors show that melanomas had high frequencies of cells that formed subcutaneous tumors, but much lower percentages of cells that formed tumors after intravenous or intrasplenic transplantation, particularly among inefficiently metastasizing melanomas. Melanoma cells in the blood and visceral organs experienced oxidative stress not observed in established subcutaneous tumors. Successfully metastasizing melanomas underwent reversible metabolic changes during metastasis that increased their capacity to withstand oxidative stress, including increased dependence on NADPH-generating enzymes in the folate pathway. Antioxidants promoted distant metastasis in NSG mice. Folate pathway inhibition using low dose methotrexate, ALDH1L2 knockdown, or MTHFD1 knockdown inhibited distant metastasis without significantly affecting the growth of subcutaneous tumors in the same mice. Oxidative stress thus limits distant metastasis by melanoma cells in vivo.

*Nature* 2015; 527: 186

Eitan Israeli