Steroid withdrawal syndrome after successful treatment of Cushing’s syndrome: a reminder

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Abstract
Steroid withdrawal syndrome (SWS) usually refers to relapse of the disease being treated after withdrawal of glucocorticoid therapy, or the symptoms of adrenal insufficiency which occur when glucocorticoids are rapidly reduced or stopped. A less well-recognised form of SWS is that which develops when patients experience a symptom complex similar to that of adrenal insufficiency despite acceptable cortisol levels. We describe three patients who presented with this form of SWS following surgical treatment for endogenous Cushing’s syndrome. All responded well to a short-term increase in the dose of glucocorticoid replacement therapy, with the median duration of the syndrome being 10 months (range 6–10 months). Trough serum cortisol levels above 100 nmol/l, with peaks between 460 and 750 nmol/l were documented in the first two patients at presentation with SWS. It is thought that the syndrome may result from development of tolerance to glucocorticoids, and mediators considered to be important in its development include interleukin-6, corticotrophin-releasing hormone, vasopressin, and central noradrenergic and dopaminergic systems. The exact underlying mechanism for SWS remains unclear. However, with increasing recommendations for use of lower doses of replacement glucocorticoids, its incidence may increase. Physicians need to be aware of this condition, which is self-limiting and easily treated by a temporary increase in the dose of glucocorticoid replacement therapy. It is possible that a slower glucocorticoid tapering regimen than that used in the standard postoperative management of patients undergoing pituitary surgery may reduce the risk of development of SWS.

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Introduction
Glucocorticoids are used to control the activity of inflammatory, autoimmune, allergic and neoplastic conditions. The term steroid withdrawal syndrome (SWS) has traditionally been used to describe the relapse of the disease being treated following withdrawal of glucocorticoid therapy (1–3). An ill-defined symptom complex with fever, anorexia, mood swings, generalised body aching, and weight loss is also recognised, occurring when supraphysiological doses of glucocorticoids are reduced rapidly to a low maintenance dose (1, 3, 4). This is due to suppression of the hypothalamo–pituitary–adrenal (HPA) axis by the glucocorticoid therapy, and with rapid reduction or cessation of treatment patients experience symptoms of hypocortisolism particularly at times of intercurrent illness or stress (5).

However, an alternative form of SWS can occur where patients experience symptoms of adrenal insufficiency despite acceptable serum cortisol levels (1, 3). We describe three patients with endogenous Cushing’s syndrome who experienced this latter form of SWS post-operatively (Table 1). All three patients responded well to a short-term increase in the dose of glucocorticoid replacement therapy.

Case 1
A 26-year-old male presented to our unit with a twelve-month history of marked obesity, high blood pressure, proximal muscle weakness and pink abdominal striae. Investigations revealed a high midnight cortisol value of 523 nmol/l (normal 50–250 nmol/l) and high urinary free cortisol (UFC: 2317 and 2084 nmol/24 h, normal < 300 nmol/24 h). His 0900 h serum cortisol was suppressed by high dose dexamethasone (2 mg four times daily for 48 h) from 682 to 37 nmol/l. Baseline adrenocorticotropic hormone (ACTH) levels were normal.
varied between 6 and 10 pg/ml (normal 5 to 50 pg/ml). A magnetic resonance (MR) scan of the pituitary gland was normal and inferior petrosal sinus sampling showed no gradient in ACTH levels between petrosal sinus and peripheral blood. A computed tomography (CT) scan of the chest and abdomen failed to identify the source of his ectopic ACTH. With a diagnosis of ectopic Cushing’s syndrome (unknown primary) he underwent bilateral adrenalectomy 16 months after the diagnosis. Histology confirmed diffuse bilateral adrenal hyperplasia without any evidence of an adenoma. Post-operatively, he was started on hydrocortisone therapy - initially 50 mg three times daily, and reducing to 10, 5 and 5 mg daily seven days after the operation when fludrocortisone (100 mcg daily) was also added. He lost weight, his muscle strength improved, and hypertension and hyperglycaemia normalised.

Within four weeks of surgery he presented with depression, fatigue, general malaise and insomnia. On examination, his blood pressure showed a postural drop of 20 mm Hg (from 115/80 mm Hg). Full blood count and biochemistry were normal, as were thyroid function tests. An insulin tolerance test showed a normal growth hormone response to hypoglycaemia but no serum cortisol response (peak 55 nmol/l), so hydrocortisone replacement was continued. A cortisol day curve on 10, 5 and 5 mg hydrocortisone was satisfactory (Fig. 1), and daytime nadir serum cortisol levels were 205 and

Table 1

<table>
<thead>
<tr>
<th>Patient characteristics.</th>
<th>Case 1 (26-year-old male)</th>
<th>Case 2 (25-year-old female)</th>
<th>Case 3 (48-year-old female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary diagnosis</td>
<td>Cushing’s syndrome – ectopic, primary unknown</td>
<td>Cushing’s disease – pituitary adenoma</td>
<td>Cushing’s syndrome – adrenal adenoma</td>
</tr>
<tr>
<td>Time of onset of SWS postoperatively (weeks)</td>
<td>4</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Approximate duration of SWS (monts)</td>
<td>10</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

Figure 1

Cortisol day curves in patient 1 (dashed line) and patient 2 (solid line) while taking 10, 5, and 5 mg hydrocortisone. Samples were taken before each dose and 2 h after the mid-day and evening doses, showing satisfactory nadir levels of serum cortisol at a time when patients had marked SWS symptoms.

Case 2

A 25-year-old female was referred for investigation of infertility. She complained of weight gain, hirsutism and oligomenorrhoea, and UFC was 274 nmol/24 h. Her midnight cortisol value was raised at 522 nmol/l and serum ACTH levels varied between 8 and 16 pg/ml. Serum cortisol was suppressed by high-dose but not low-dose dexamethasone. A pituitary MR scan showed a normal sized pituitary gland with no evidence of an adenoma. On inferior petrosal sinus sampling, the central-to-peripheral gradient of ACTH increased from 11.5 at baseline to >25 on the left side following administration of corticotrophin-releasing hormone (CRH). She underwent transsphenoidal surgery a year after diagnosis. Histology confirmed the removal of a corticotroph adenoma with some normal anterior pituitary tissue. She was started on 150 mg hydrocortisone in three divided doses, which was titrated down to 10, 5 and 5 mg daily within seven days of surgery. Initially she felt well, but about 3 weeks after surgery she started to feel lethargic, and experienced insomnia, restlessness and tremor. Baseline haematology, biochemical profile, and thyroid function were normal. An insulin tolerance test showed a normal growth hormone response to hypoglycaemia but no serum cortisol response (peak 55 nmol/l), so hydrocortisone replacement was continued. A cortisol day curve on 10, 5 and 5 mg hydrocortisone was satisfactory (Fig. 1), and daytime nadir serum cortisol levels were 205 and
155 nmol/l. Considering the possibility of SWS, her dose was increased to 20, 10 and 10 mg daily and within two weeks she felt much better. Over the next six months we slowly reduced the dose of hydrocortisone without any relapse of her symptoms.

**Case 3**

A 48-year-old female presented with a six-month history of weight gain, proximal muscle weakness, generalised fatigue, facial plethora and multiple bruises. Her clinical appearance was suggestive of Cushing’s syndrome, UFC was 1510 nmol/24 h, and morning serum cortisol was 788 nmol/l, with a midnight value of 479 nmol/l. Plasma ACTH was < 5 ng/l. Serum cortisol failed to suppress with high dose dexamethasone and a CT scan of the abdomen showed a 2.5 cm mass in the right adrenal gland. She was discharged seven days after right adrenalectomy, taking 30 mg hydrocortisone twice daily. The dose of hydrocortisone was reduced gradually over the subsequent two months to 10, 5 and 5 mg daily. She then complained of intolerable restlessness, tremor, increased sweating, palpitations, anorexia, generalised aches and irritability over a two-week period. ECG showed sinus tachycardia with a rate of 120/min, thyroid function tests were normal. On 10, 5 and 5 mg hydrocortisone her 24-h UFC varied between 185 and 255 nmol/24 h. Again with a presumptive diagnosis of SWS, the dose of hydrocortisone was increased to 20, 10 and 10 mg daily with a dramatic symptomatic improvement. The dose was gradually reduced over the following 10 months to a maintenance dose of 10, 5, 5 mg. She remains well on this dose three years after initial presentation.

**Discussion**

Four aspects of glucocorticoid withdrawal are important, whether occurring after cessation of therapeutic doses of glucocorticoids or after successful treatment of endogenous glucocorticoid excess, namely: (i) relapse of the disease for which the drug was originally prescribed, (ii) suppression of the HPA axis, which can occur for a variable length of time (iii) psychological dependence, and (iv) a non-specific withdrawal syndrome occurring in the setting of adequate circulating cortisol levels (3), as occurred in our three patients. Although the symptomatology of SWS is similar to that of adrenal insufficiency, it is not identical, since a mixed picture occurs consisting of both hormone deficiency as well as a generic withdrawal syndrome (3).

Howlett, in discussing hydrocortisone replacement for adrenal insufficiency, advocated that the UFC and 0900 h serum cortisol values should be within the reference range for the normal population (to avoid over-replacement) and 1230 h and 1730 h serum cortisol values should be above 50 nmol/l, preferably above 100 nmol/l (to avoid under-replacement) (6). In our first two patients we have clearly documented serum cortisol levels above this cut-off at the time of presentation with SWS (Fig. 1). A therapeutic trial of a higher dose of hydrocortisone was beneficial and in the first case symptoms relapsed when we tried to taper the dose of hydrocortisone too rapidly. We believe all 3 patients had developed SWS following successful surgical treatment of prolonged endogenous hypercortisolism (Table 1).

The form of SWS that we have described, characterised by anorexia, nausea, lethargy, fever, arthralgia, skin desquamation, weakness, postural hypotension, vomiting and weight loss, was recognised as early as 1960, although the exact mechanism of action is not clear, nor is its prevalence (3, 4, 7, 8). Suppression of the HPA axis by the hypercortisolaemic state, whether endogenous or exogenous, was initially thought to be responsible, until the axis was shown to be normal in these patients, with normal baseline cortisol levels (7). Subsequently, Amatruda et al. demonstrated some suppression of the HPA axis in these patients but, importantly, serial plasma and urine steroid levels were within normal limits, and there was no correlation between the status of the HPA axis and the severity or duration of SWS (4). Hence the condition was attributed to a state of ‘relative adrenal insufficiency’ as tissues had been exposed to high levels of steroids for a prolonged period. It is thought that these individuals develop tolerance to glucocorticoids, such that the replacement doses used are inadequate to allow correct functioning of the central nervous system and other organs (3). Tyrrell describes the possibility of a relative state of glucocorticoid resistance in these patients, effectively rendering them hypoadrenal (8). In more recent studies, a rise in the level of interleukin-6 (IL-6) has been linked with the acute form of SWS occurring immediately after surgery for Cushing’s syndrome in patients who were hypocortisolaemic, and a similar symptom complex was noted after infusion of IL-6 (9, 10). Papanicolaou et al. found that even by day 9 or 10 postoperatively, when these patients were on glucocorticoid replacement, IL-6 levels decreased but were not back to normal (9). Alterations in the concentrations of a number of other mediators have been hypothesised to play a role in the development of the SWS, notably CRH and central noradrenergic and dopaminergic systems, reviewed in more detail by Hochberg et al. (3).

There are few specific recommendations in standard endocrinology textbooks and the medical literature regarding the rate at which glucocorticoid therapy should be reduced following successful surgical treatment of Cushing’s syndrome. Orth and Kovacs recommend that 200 mg hydrocortisone be given over the first 24 h after surgery, then ‘100 mg, 75 mg, 50 mg and maintenance hydrocortisone (10 to 25 mg each morning) on successive days thereafter’
Miller and Tyrrell state that postoperative hydrocortisone replacement is ‘reduced to maintenance doses (30 mg per day) by the seventh to tenth day’ (12). However, in a Cushing’s Newsletter, Cook (13) has suggested the administration of 60–80 mg hydrocortisone for 2 weeks, followed by a reduction of 10–20 mg every 10–14 days until a maintenance dose is reached. There is, therefore, considerable variation amongst endocrinologists regarding recommendations for the tapering of glucocorticoids.

The patients we have described, particularly the first two cases, provide a useful reminder of the need for more gradual tapering of glucocorticoid doses to a maintenance level in the setting of successfully treated Cush- ing’s syndrome, in order to reduce the risk of development of SWS postoperatively. Concerned about potential long-term side effects of glucocorticoids, endo- crinologists increasingly recommend lower doses of replacement glucocorticoids (6, 14), and consequently the risk of SWS is increased. Furthermore, hypoadrenal- ism is the most potent stimulus to recovery of ACTH secretion postoperatively in pituitary-dependent Cush- ing’s syndrome (15), thus most physicians will aim to decrease the steroid dose to the lowest tolerated mainte- nance level as quickly as possible. However, patients with Cushing’s syndrome have usually been hypercortisolaemic for a prolonged period prior to surgery; a few additional weeks of high serum cortisol levels secondary to ‘over-treatment’ with replacement hydrocortisone postoperatively may therefore be preferable to the mor- bidity associated with SWS. In our third patient, how- ever, despite a gradual tapering of glucocorticoid therapy to maintenance levels over a two-month period following unilateral adrenalectomy, SWS still occurred.

In conclusion, although the exact mechanism of SWS is not clear, physicians involved in the manage- ment of endogenous or exogenous steroid excess need to be aware of this condition. Caution must be exercised by endocrinologists regarding the rate at which they initially reduce replacement glucocorticoid therapy follow- ing successful surgery for Cushing’s syndrome. It is possible that a slower tapering regimen than that used in the standard postoperative management of patients undergoing pituitary surgery may reduce the chances of SWS. Pre-operative normalisation of cortisol secretion using gradually increasing doses of medical therapy to suppress steroidogenesis may also be ben- eficial in preventing later SWS. However, it is important to remember that SWS is a self-limiting state, and should it occur, its management should include a tem- porary increase in the dose of glucocorticoids, followed by slow tapering to a maintenance dose.

References