Delayed cure of Cushing’s disease after transsphenoidal surgery of pituitary microadenomas

Report of two cases

STEPHEN D. MCDONALD, M.D., STANLEY E. VON HOFE, M.D., STEVEN G. DORFMAN, M.D., RICHARD M. JORDAN, M.D., JAMES R. LAMORGESE, M.D., AND ROBERT L. YOUNG, M.D.

Divisions of Endocrinology and Neurosurgery, United States Air Force Medical Center, Lackland Air Force Base, Texas

Transsphenoidal microdissection has been proposed as a preferred means of treating Cushing’s disease. This procedure allows the surgeon to remove a pituitary microadenoma and at the same time to preserve normal tissue. Two cases described here were treated by this method. An interesting and important observation was that neither patient appeared to be cured for 2 to 6 weeks after surgery, as assessed by dexamethasone suppression. Later, normal suppressibility occurred and the course of each patient was compatible with cure. Patients treated by this method should not be automatically retreated because of adrenocorticotrophic hormone (ACTH) non-suppressibility in the early postoperative period.

KEY WORDS • pituitary neoplasm • hypophysectomy • 17-hydroxycorticosteroids • Cushing’s disease

Recent findings indicate that a majority of patients with Cushing’s disease have adrenocorticotrophic hormone (ACTH)-secreting microadenomas. Transsphenoidal surgery provides an attractive method of removing these microadenomas while leaving the remainder of the gland intact. The popularity of this form of therapy has been bolstered by many reports of its efficacy. Most recently Tyrrell, et al., have demonstrated cure in 16 of their 17 patients with Cushing’s disease who underwent selective microadenoma removal. Early assessment of the hypothalamic-pituitary-adrenal axis after pituitary surgery is difficult, due to the routine use of cortisone postoperatively. The standard serum and urinary cortisol measurements to define cure of the hypercortisolism are invalidated by the exogenous administration of the cortisone. We report two patients with Cushing’s disease treated by transsphenoidal surgery who received only dexamethasone in the postoperative period. This gave us an opportunity to study the early postoperative hypothalamic-pituitary-adrenal dynamics.
Neither patient demonstrated normal pituitary ACTH suppression after dexamethasone in the first few weeks after surgery. Later in their course, however, both patients regained suppressibility that was compatible with cure. Appreciation of this fact would hopefully prevent additional surgery or radiation therapy in a patient who had adequate initial therapy.

**Case Reports**

**Case 1**

This 32-year-old man presented with a 3-year history of hypertension. For 1 year he had noticed weight gain, weakness, facial fullness, skin striae, easy bruising, and decreased libido. Physical examination demonstrated centripetal obesity, wide violaceous striae, and marked proximal muscle weakness. Blood pressure was 140/100. He had absent diurnal variation of serum cortisol: the morning value was 22 μg/dl and the evening was 20 μg/dl. The urinary free cortisol was markedly elevated at 1114 μg/24 hrs (normal values: 100 to 400 μg/24 hrs, BioScience Laboratories, Van Nuys, California). With high-dose dexamethasone testing, the urinary free cortisol suppressed to 138 μg/24 hrs. He demonstrated an exaggerated response to a standard metyrapone test by raising the urinary 17-hydroxycorticosteroids (17-OCHS) from 32 to 120 mg/24 hrs (normal values: 4 to 12 mg/24 hrs). These tests were diagnostic of Cushing's disease.

Sellar tomography showed anterior floor demineralization of a normal-sized sella. The carotid arteriogram showed a right anterior sella tumor stain. A pituitary chromophobe microadenoma, 4 × 4 mm in size, was removed by transsphenoidal microdissection.

Serum cortisol and urinary 17-OCHS did not suppress normally for at least 12 days postoperatively (Table 1). A cortisol determination on Day 30 was not detectable, which suggested that cure had occurred in the interim period. Detailed evaluation of pituitary function during the 6-month period after surgery revealed T4 (by radioimmune assay) = 5.3 μg/dl (5 to 12 μg/dl), T3 resin uptake + 25% (25% to 35%), and thyroid stimulating hormone (TSH) <1 (1 to 5 μU/ml); follicle stimulating hormone (FSH) = 11 mIU/ml (4 to 25 mIU/ml), luteinizing hormone (LH) = 7 mIU/ml (less than 7 mIU/ml), and a testosterone level of 3.5 ng/ml (4 to 10 ng/ml). Insulin hypoglycemic testing (nadir plasma glucose 54 mg%) elicited a rise in serum cortisol from 0.44 to 6.8 μg/dl, an increase in serum prolactin from 16 to 100 ng/ml, and maximum growth hormone rise to 6.4 ng/ml. At his 6-month follow-up visit the patient demonstrated improved muscle strength, a 20-lb weight loss, and improvement in blood pressure control. Replacement therapy consisted of cortisone and thyroxine.

**Case 2**

This 32-year-old woman presented with a 2-year history of hypertension, amenorrhea, and hypothyroidism. She was receiving thyroid replacement and anti-hypertensive medication. Leg weakness and low-back pain had been present for 1 month. Physical examination revealed truncal obesity, facial fullness, severe proximal muscle weakness, and moderate hypertension. Hypokalemia with potassium levels of 2.7 mEq/liter was present and difficult to correct with potassium replacement. She had elevated morning and evening serum cortisols, 36 and 48 μg/dl, respectively. Following a 1-mg overnight dexamethasone suppression test the serum cortisol remained elevated at 52 μg/dl. With a standard low-dose 2-mg dexamethasone test the urinary 17-OCHS were suppressed from 32 to 20 mg/24 hrs, and further suppressed to 2 mg/24 hrs with a high-dose 8-mg dexamethasone test. With a standard metyrapone test, the urinary 17-OCHS increased from 40 to 70 mg/24 hrs. These tests were diagnostic of Cushing's disease. Lumbar spine films demonstrated marked demineralization with multiple vertebral compression fractures. Polytomography of the sella turcica revealed antero-inferior bulging of the sella floor to the right of the midline, although overall sella size was normal.

At transsphenoidal surgery, failure to identify a distinct microadenoma led to an attempt at total hypophysectomy. It was necessary, however, to leave a small amount of tissue behind because of its close proximity to the cavernous sinus. Biopsy of this tissue revealed it to be chromophobe adenoma.

Serum cortisol was not normally suppressed on Days 1 and 5 postoperatively (Table 1). Although the cortisol was low on Day 10, the urinary 17-OCHS were not in the
Delayed response to transsphenoidal pituitary surgery

TABLE 1

Postoperative dexamethasone testing*

<table>
<thead>
<tr>
<th>Time postop (days)</th>
<th>A.M. Serum Cortisol (µg/dl)</th>
<th>Urinary 17-OHCS (mg/24 hrs)</th>
<th>Dexamethasone Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0†</td>
<td>22</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>8.2</td>
<td>12</td>
<td>1 mg/12 hrs</td>
</tr>
<tr>
<td>12</td>
<td>6.5</td>
<td>9</td>
<td>0.5 mg/12 hrs</td>
</tr>
<tr>
<td>30</td>
<td>undetectable</td>
<td>--</td>
<td>0.5 mg/12 hrs</td>
</tr>
<tr>
<td>Case 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0†</td>
<td>52</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>--</td>
<td>2 mg/2 hrs</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>--</td>
<td>2 mg/6 hrs</td>
</tr>
<tr>
<td>10</td>
<td>2.5</td>
<td>17</td>
<td>1 mg/6 hrs</td>
</tr>
<tr>
<td>40</td>
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<td>4</td>
<td>0.5 mg/12 hrs</td>
</tr>
<tr>
<td>180</td>
<td>1.0</td>
<td>2</td>
<td>0.5 mg/6 hrs</td>
</tr>
</tbody>
</table>

*Normal suppression = serum cortisol < 5 µg/dl after 1 mg dexamethasone and/or urinary 17-hydroxycorticosteroid (17-OHCS) determination < 4 mg/24 hrs on 2 mg dexamethasone daily.
†Values before surgery (baseline).

suppressed range. The patient was maintained on 1 mg of dexamethasone per day, but as late as 40 days after surgery there was still evidence of non-suppressibility (Table 1). Clinical improvement was noted about 3 months after surgery, manifested by normokalemia, increased muscle strength, and more easily controlled hypertension. The dexamethasone was then discontinued.

At the 6-month follow-up visit the 8:00 a.m. cortisol was 8.2 µg/dl. The urinary 17-OHCS excretion was 6 mg/24 hrs, and rose to 11 mg/24 hrs after metyrapone. There was normal suppression with dexamethasone (Table 1). Serum growth hormone levels were less than 1 ng/ml before and during insulin hypoglycemia testing. The patient still had amenorrhea and mild hypertension.

Discussion

Both our patients failed to demonstrate normal suppression of serum cortisol and urinary 17-OHCS after dexamethasone administration for at least 2 weeks after surgery. There was no evidence of infection or other identifiable stress which could explain this lack of suppression. Case 1 had an abnormal suppression at the 12th day after operation, but an apparently normal one by the 30th day. Case 2 had questionable response as late as the 40th postoperative day. The reason for the slow return to normal of pituitary ACTH suppressiveness in these patients is unknown. One would expect nondetectable blood cortisol concentration within a day of removal of an autonomous ACTH-secreting tumor. Although speculative, it is possible that progressive infarction of residual tumor explains the phenomena of delayed cure seen in our patients. A similar course associated with infarction of an ACTH-secreting microadenoma following radiation therapy was recently described by Cook, et al.1

The unexpected finding in Case 2 of postoperative non-suppressibility even with high-dose dexamethasone would also support our hypothesis that following the pituitary surgery there was a progressive infarction of tissue with release of ACTH. Since the ACTH release is secondary to tissue damage and not just autonomous secretion, one would not expect cortisol suppression with high-dose dexamethasone. Schnall, et al.5 also implied a gradual return to normal suppressibility over an 18-month period in their patient with Cushing’s disease who was treated by transsphenoidal microdissection, but those authors did not speculate as to the cause.

Our data suggest that a successful outcome of transsphenoidal surgery for Cushing’s disease is not necessarily dependent upon normal pituitary suppressiveness in the early postoperative period. This fact must be emphasized, since further surgery and/or radiation therapy might be recommended to a patient who had a non-suppressible serum cortisol or urinary hydroxycorticosteroids several weeks after surgery. We suggest that such a patient be followed closely without major intervention for several weeks at least, assuming the clinical condition of the patient does not indicate the need for further immediate therapy.

References

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*Address reprint requests to: Major Robert L. Young, USAF, MC, Wilford Hall, USAF Medical Center/SGHME, Lackland AFB, Texas 78236.*