Surgical management of adrenocorticotropic hormone–secreting macroadenomas: outcome and challenges in patients with Cushing’s disease or Nelson’s syndrome

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Object. Adrenocorticotropic hormone (ACTH)-secreting pituitary macroadenomas are an uncommon cause of Cushing’s disease (CD) and, subsequently, Nelson’s syndrome (NS). They have been associated with low postoperative remission rates. The outcome of modern surgical treatment is unclear and thus was assessed in a series of 43 patients, with the goal of improving therapeutic results in patients with ACTH-secreting macroadenomas.

Methods. Thirty-seven patients presented with CD and six with NS. They represented 15% of the patients surgically treated at the authors’ institution for ACTH-secreting adenomas. The median patient age was 38 years (range 14–71 years), and the mean duration of follow up was 37 months (range 1–108 months).

Remission occurred in 25 (67.6%) of 37 patients with CD, whereas the disease persisted in 12 (32.4%) of 37 patients. After an initial remission, three (12%) of 25 patients demonstrated signs and symptoms indicative of disease recurrence. Among patients with NS, only one (16.6%) displayed remission. Invasion of the dura mater by tumor was histologically demonstrated in 10 patients with CD and in two patients with NS.

Conclusions. Comprehensive management of CD caused by ACTH-secreting macroadenomas through the appropriate use of combination therapy, including surgery, radiotherapy, radiosurgery, and adrenalectomy, can lead to outcomes similar to those for microadenomas. Disease recurrence and persistence rates are higher, often because of the invasiveness associated with macroadenomas. Remission of NS-associated macroadenomas is difficult to achieve. Strategies for the characterization and treatment of invasive macroadenomas are needed.

KEY WORDS • Cushing disease • macroadenoma • Nelson syndrome • adrenocorticotropic hormone–secreting adenoma • transsphenoidal surgery

A DRENOCORTICOTROPIC hormone–secreting macroadenomas are an uncommon cause of CD. The majority of patients with this disease have pituitary microadenomas, that is, small intrasellar tumors less than 10 mm in diameter. The relatively low incidence of ACTH-secreting macroadenomas, the prolonged period preceding the onset of obvious symptoms, and the aggressive behavior exhibited by most of these lesions explain why they still represent a major challenge in the management of pituitary disease. Differences in the biochemical pattern and the clinical presentation between micro- and macroadenomas have been previously examined1,6,7,12 and in part help to explain why macroadenomas usually demonstrate a more aggressive clinical course.

Transsphenoidal surgery remains the initial treatment of choice for pituitary-dependent CD but is not always capable of providing complete and permanent remission of the disease; the use of adjunctive therapies is often required to achieve a satisfactory outcome. Repeated surgery, medical treatment, and radiotherapy (stereotactic or conventional) are used as safe and efficacious treatments following an initial surgery. As a definitive option in the management of these tumors, total bilateral adrenalectomy may be performed in patients in whom other therapies have failed.10,13 This treatment, although reliable in normalizing cortisol secretion, is sometimes (10–40%) followed by the development of NS when the autonomous pituitary gland receives inadequate glucocorticoid feedback from the replacement steroid. Nelson’s syndrome–associated macroadenomas are often more aggressive than the ACTH-secreting macroadenomas that cause CD.7

Clinical Material and Methods

Patient Population

We retrospectively reviewed the records of 43 patients with symptomatic ACTH-secreting macroadenomas treated surgically at a single institution by a single surgeon (E.R.L.) between 1994 and 2003. These patients represented 15% of those surgically treated for CD. Thirty-seven (86%) presented with signs and symptoms of CD; the other six (14%) were referred to our institution because signs and symptoms

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CD = Cushing’s disease; GKS = gamma knife surgery; IPSS = inferior petrosal sinus sampling; NS = Nelson’s syndrome; TSS = transsphenoidal surgery; UFC = urinary free cortisol.
of NS developed after the patient had undergone bilateral adrenalectomy for unsuccessfully treated CD. The median patient age was 38 years (range 14–71 years). The mean follow-up duration was 37 months (range 1–108 months). The majority (32 of 43) of patients were women, with only 11 men in the series. The mean duration of symptoms before diagnosis was 65 months (range 2–348 months). Age, sex, and duration of symptoms in the two groups are shown in Table 1. The signs and symptoms on presentation are shown in Tables 2 and 3.

**Endocrine Evaluation**

Diagnostic endocrinological examinations were performed in the two groups of patients. All those with CD had excess cortisol secretion. Elevated 24-hour UFC was demonstrated in 91% of the patients. These results were confirmed by measuring serum cortisol and ACTH, which were assessed in 95 and 78.4% of the patients, respectively. Based on abnormal ACTH levels and plasma and salivary cortisol determinations, CD was diagnosed in the three patients who had presented with symptoms and signs of Cush- ining’s syndrome but normal UFC levels. In one case, IPSS was performed to confirm the diagnosis, which was necessary because the patient had previously undergone surgery and was found to harbor a non–ACTH-staining pituitary adenoma. Results of the IPSS confirmed the pituitary origin of the excess ACTH secretion. The IPSS findings were helpful in another patient whose surgically manipulated tumor stained for prolactin only and not ACTH. In this case the IPSS results also confirmed the pituitary origin of the ACTH secretion. In the patients with NS, the diagnosis was based on the presence of high ACTH levels and hyperpigmentation. In both patient groups we performed a comprehensive evaluation of pituitary function.

**Preoperative Imaging**

The second step in the diagnostic process was to obtain imaging results in support of the laboratory data. Magnetic resonance imaging studies were performed in all the patients except one who had a cardiac pacemaker (she underwent computerized tomography scanning). Extrasellar extension of the tumor was demonstrated in 10 (27%) of 37 patients with CD and in two (33.3%) of the six patients with NS. Only one macroadenoma, in a patient with CD, was clearly cystic. We systematically evaluated tumor size in both groups: in the patients with CD, the mean tumor diameter was 2.5 cm, ranging from 1 cm to an exceptional diameter of 13 cm; in the patients with NS, the mean lesion diameter was 2.1 cm (range 1.5–2.7 cm).

**Surgery and Complications**

Surgery was the first treatment in all patients. Different techniques were used, depending on the various preoperative findings. The transphenoidal approach was preferred in all patients, although one patient underwent a craniotomy because the tumor had major extrasellar extension and involved both carotid arteries intracranially. Although an intraoperative cerebrospinal fluid leak occurred in 43% of the patients with CD and in 50% of those with NS, the defect was routinely repaired with an intraoperative fat graft. A postoperative cerebrospinal fluid leak occurred in only one case.
Cushing’s macroadenoma

TABLE 4
Complications in patients with ACTH-secreting macroadenomas*

<table>
<thead>
<tr>
<th>Complication</th>
<th>CD</th>
<th>NS</th>
</tr>
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<tbody>
<tr>
<td>postop CSF leak</td>
<td>1 (2.7)†</td>
<td>0</td>
</tr>
<tr>
<td>nasal septal perforation</td>
<td>4 (10.8)‡</td>
<td>0</td>
</tr>
<tr>
<td>vascular injury</td>
<td>1 (2.7)§</td>
<td>0</td>
</tr>
<tr>
<td>diabetes insipidus</td>
<td>8 (21.6)∥</td>
<td>0</td>
</tr>
<tr>
<td>transient CN III palsy</td>
<td>1 (2.7)</td>
<td>0</td>
</tr>
<tr>
<td>SIADH</td>
<td>2 (5.4)</td>
<td>1**</td>
</tr>
<tr>
<td>DVT/pulmonary embolus</td>
<td>1 (2.7)</td>
<td>0</td>
</tr>
</tbody>
</table>

* CN = cranial nerve; DVT = deep venous thrombosis; SIADH = syndrome of inappropriate antidiuretic hormone.
† Condition preexisted in one patient.
‡ At the patient’s second craniotomy.
§ Five cases were transient and three cases were permanent.
** Accompanied by seizures.

Table 4: Complications in patients with ACTH-secreting macroadenomas

Pathological Features

The pathological analysis included immune histochemical studies in all cases and ultrastructural analysis in most. A dural biopsy procedure was performed in 23 (62%) of 37 patients with CD and in four (66%) of the six patients with NS. Dural invasion was demonstrated histologically in 43% of those with CD and in 75% of those with NS. Adrenocorticotrophic hormone positivity was confirmed in 34 of 37 patients with CD. In the remaining three, no tumor was found in one case, the lesion did not stain for ACTH in another (ultimately proven to be a carcinoid metastasis), and the lesion stained for prolactin only in another case. This latter case prompted an IPSS study whose results confirmed the pituitary origin of excess ACTH secretion and led to GKS.

In the patients with CD, no perioperative corticosteroid medication was administered. Plasma cortisol was systematically measured postoperatively every 6 hours to assess serum cortisol levels. Cortisol replacement therapy was initiated when cortisol levels decreased to 3 μg/dl or less. On subsequent follow-up, UFC was assessed in 68% of the patients, plasma cortisol in 73%, and ACTH in 62%. We considered CD to be in remission when UFC, ACTH, or plasma cortisol were within the normal range. Remission of NS occurred when serum ACTH was less than 50 pg/ml. Patients in both groups underwent regular (usually annual) pituitary imaging studies. The absence of a progressively enlarging sellar/parasellar mass was a requirement for considering a disease to be in remission.

Patients with CD that did not abate postoperatively were considered for adjunctive therapy. In patients with mild clinical manifestations who could tolerate suppressive treatment with ketoconazole, GKS or conventional radiotherapy (for large-volume residual lesions) was usually recommended. In patients who were severely ill from CD or who were intolerant of ketoconazole, bilateral adrenalectomy was generally recommended.

Patients with uncontrolled NS were treated with radiotherapy or radiosurgery when possible and with repeated surgery when necessary.

Results

The first choice of treatment was TSS in all of the patients, except one who underwent a craniotomy. The relatively low complication rate in this study reflects the safety of this technique in the hands of an experienced team. New postoperative hormonal deficits (Fig. 1) requiring replacement therapy were uncommon, indicating that selective microsurgical removal of the tumor can often be accomplished while preserving the integrity and function of the normal gland. The different biological and clinical aspects of the two diseases led us to examine them separately. The larger group consisted of patients with CD. We divided these patients further into two subgroups based on whether prior surgery had been performed at another institution.

Among patients who did undergo previous surgical therapy for CD (26 patients), the major positive prognostic factor was a significant early postoperative decrease in plasma cortisol levels (adrenal insufficiency was defined as plasma cortisol < 3 μg/dl during the first 2–3 days after surgery; Fig. 2). Twelve (46.2%) of 26 patients had symptoms of adrenal insufficiency; among these, eight (66.6%) experienced remission without additional therapy. Four patients (33.3%), after an initial remission, suffered disease recurrence; among these, two had not undergone other therapies at the time of our analysis, whereas the other two had undergone a second TSS resulting in another remission. In one of these latter cases, GKS was also performed. The remission rate in patients who demonstrated adrenal insufficiency following surgery was 66.6% (eight of 12 patients). The disease abated in two more patients after adjunctive therapies, for an ultimate remission rate of 83.3% (10 of 12 patients) in this group.
Cortisol levels did not decrease in the first 2 or 3 days after initial surgery in 14 (53.8%) of 26 patients. Nevertheless, in six patients (42.8%) the disease abated 6 weeks to 12 months later. In one patient GKS was performed because of suspicious magnetic resonance imaging findings. At the most recent follow up (66 months postsurgery), one of these six patients presented with disease recurrence and has not yet undergone additional therapy. The remaining eight patients whose cortisol levels did not significantly decrease required adjunctive therapies. Of the seven patients who received subsequent therapy, four were treated with GKS and remission occurred in only one; adrenalectomy was performed in two of the three patients with persistent disease. Three patients underwent conventional radiotherapy; disease remission occurred in only one of these patients. The ultimate remission rate in patients without postoperative adrenal insufficiency was seven (50%) of 14, five experiencing remission soon after surgery. Remission occurred in two more patients after adjunctive therapies.

The rate of remission in patients with CD after initial surgery was higher in those whose tumors did not invade the dura mater (70.6%) compared with those in whom the dura mater was clearly invaded (55.5%).

Eleven of the 37 patients with CD had previously undergone treatment before being referred to the pituitary center at the University of Virginia Health System (Fig. 3). In this subgroup postoperative adrenal insufficiency occurred in only two patients (18.2%). One patient experienced remission after surgery and one required subsequent GKS because of disease persistence. The only treatment both of these patients had received at other institutions was TSS (performed twice in one patient). The remaining nine patients (81.8%) did not have adrenal insufficiency after surgery. All of them were treated with adjunctive therapies, as listed in Table 6. The initial postoperative remission rate in these patients was 11% (one of nine patients). In one patient remission was subsequently achieved after adjunctive radiotherapy and in two others after successful bilateral adrenalectomy. Thus, the ultimate remission rate following adjunctive therapies was 44% (four of nine patients).

The group with NS consisted of six patients, all of whom had undergone previous treatment (Fig. 4). All were treated initially at our institution with TSS and underwent adjunctive therapies (Table 7). In only one patient did the disease abate, as defined by normalization of ACTH levels. Durval invasion was observed in three (50%) of six patients with NS.

**Discussion**

The management of CD, especially when caused by ACTH-secreting pituitary macroadenomas, still represents a formidable challenge for neurosurgeons and clearly requires a specialized approach to achieve the goal of endocrinological remission. Despite the large size of these tumors, the transsphenoidal surgical approach, especially if performed using modern techniques, still represents the best treatment to reach the goals of gross-total removal of the tumor and relief of mass effect. From a clinical viewpoint, symptoms typical of CD were present in the majority of the patients in our study and included physical (weight gain, central fat deposition, hirsutism, purple striae, and so forth) and often psychological symptoms. Documented visual loss occurred in 13.5% of the patients with macroadenoma-associated CD, but episodes of blurred vision were frequent in patients with either CD or NS. Note that the reported incidence of visual problems was greater in the patients with macroadenoma-associated NS, which seems to be in line with the lesion’s well-documented aggressive behavior.7,10 The median duration of symptoms before diagnosis was 3 years. A late diagnosis affects prognosis given that the reported success rate in different series2,4 is higher if tumors
Cushing’s macroadenoma

are treated when smaller. Magnetic resonance imaging represents the best means of visualizing the sellar region and can be considered a reliable guide for surgeons before and during the operation. Extrasellar extension was demonstrated in 27% of patients with CD and in 33% of those with NS.

The importance of IPSS has been highlighted in the literature, especially in the management of microadenomas. Given the large size of the tumors in the patients in the present analysis, IPSS was performed in only two because the specimens from a prior surgery did not stain for ACTH; in both of these patients it was helpful to confirm the pituitary origin of ACTH secretion. According to the literature and the results we reported, surgery is usually the best means of inducing prompt remission.

Adjunctive therapies are often needed in the subsequent treatment of these patients. Given the spectrum of available therapies, a rational approach informed by the advice of an experienced team of surgeons, endocrinologists, radiologists, and radiation oncologists must be followed. In our experience the most reliable postoperative parameter to predict the outcome in patients with CD was the plasma cortisol level in the immediate postoperative period. A cortisol level less than 3 μg/dl (adrenal insufficiency) and associated with symptoms of hypocortisolism indicated that remission was likely and that interim cortisol replacement was needed. In such cases oral hydrocortisone was administered. When a cortisol decrease was not detected, the patients were discharged after being carefully informed of the symptoms of hypocortisolism that might require replacement therapy. In the patients with postoperative adrenal insufficiency was predictive of a good outcome. Eight of 14 patients who did not experience a postoperative decrease in plasma cortisol suffered persistent disease and required adjunctive treatment. In the patients who demonstrated initial remission of the disease followed by a recurrence, repeated TSS was the best course of action. In patients with persistent disease, the preferred treatment was radiotherapy in the form of conventional radiotherapy or GKS. Despite this additional management, remission occurred in only two patients. The ultimate overall remission rate in patients with macroadenoma-associated CD was 59.5%. This result demonstrates that in the management of macroadenoma-associated CD, a satisfactory success rate can be achieved, especially when a single experienced team follows up the patients. The ultimate treatment option, usually recommended when other modalities have failed, is bilateral adrenalectomy. Unfortunately, this treatment, which reliably lowers plasma cortisol, is sometimes followed by the development of NS. We evaluated six patients with NS who were examined at our institution between 1994 and 2003. These patients were treated using several different approaches, but remission occurred in only one patient. Pituitary macroadenomas within the context of NS are exceedingly difficult to control.

Conclusions

This group of ACTH-secreting pituitary macroadenomas represents an extremely interesting and difficult therapeutic challenge. Many of these tumors are invasive, and the outcome in patients with uncontrolled CD or NS is often less than ideal. The disease and its current management are well characterized by this and other reports in the literature. What is needed, however, is a way to provide growth control and hormonal control in these tumors, perhaps with the use of new pharmacotherapeutic approaches.

Acknowledgment

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### TABLE 6

<table>
<thead>
<tr>
<th>Case No.</th>
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<th>Adjunctive Therapy</th>
<th>Outcome</th>
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<tr>
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<td>adrenalectomy†</td>
<td>remission</td>
</tr>
<tr>
<td>2</td>
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<td></td>
<td>remission</td>
</tr>
<tr>
<td>3</td>
<td>TSS, GKS</td>
<td></td>
<td>remission</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>TSS, GKS</td>
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<td>remission</td>
</tr>
<tr>
<td>9</td>
<td>TSS, GKS</td>
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<td>remission</td>
</tr>
</tbody>
</table>

† XRT = radiotherapy.
† Patient refused GKS.
† Six years remission.

### FIG. 4

Chart demonstrating outcome in patients with NS.

### TABLE 7

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Previous Therapy</th>
<th>Adjunctive Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>adrenalectomy</td>
<td>GKS</td>
<td>persistence</td>
</tr>
<tr>
<td>2</td>
<td>adrenalectomy</td>
<td>GKS</td>
<td>persistence</td>
</tr>
<tr>
<td>3</td>
<td>adrenalectomy, TSS, GKS</td>
<td>GKS</td>
<td>persistence</td>
</tr>
<tr>
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<td>TSS</td>
<td>persistence</td>
</tr>
<tr>
<td>5</td>
<td>TSS, XRT, &amp; adrenal-ectomy</td>
<td>TSS, GKS, &amp; GKS</td>
<td>persistence</td>
</tr>
<tr>
<td>6</td>
<td>TSS, XRT, &amp; adrenal-ectomy</td>
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<td>remission</td>
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