**Management of Cushing’s disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging**

**Clinical article**

**Daniel M. Prevedello, M.D.,1 Nader Pouratian, M.D.,2 Jonathan Sherman, M.D.,2 John A. Jane Jr., M.D.,2 Mary Lee Vance, M.D.,3 M. Beatriz Lopes, M.D.,4 and Edward R. Laws Jr., M.D.5**

1Department of Neurological Surgery, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania; Departments of 2Neurosurgery, 3Internal Medicine (Division of Endocrinology), and 4Pathology, University of Virginia Health System, Charlottesville, Virginia; and 5Department of Neurosurgery, Stanford University Medical Center, Palo Alto, California

**Object.** Outcomes of therapy for Cushing’s disease (CD) vary depending on different aspects of presentation and diagnostic studies. The authors designed this study to verify the remission rate and outcomes after transsphenoidal surgery (TSS) for patients with CD who had positive findings on MR imaging.

**Methods.** Patients who had presented with CD at the University of Virginia for initial treatment between July 1992 and December 2005 were retrospectively reviewed. The patients included in the study were considered to be optimal surgical candidates, defined as an adult (> 18 years of age) with classic clinical features of CD, laboratory studies confirming a central (pituitary/hypothalamic) adrenocorticotropic hormone–dependent source of disease, and an MR imaging study revealing a microadenoma in the sella turcica.

**Results.** A total of 167 patients fulfilled the criteria. Thirty were men (18%) and 137 were women (82%). The mean age was 42.3 years (range 18.2–77 years). All patients underwent TSS. Surgical remission was achieved in 148 patients (88.6%), which was correlated with the surgeon’s intraoperative identification of an adenoma (p = 0.03). Histopathological confirmation of an adrenocorticotropic hormone–secreting adenoma strongly correlated with remission (p = 0.0001). Three patients (1.8%) had postoperative cerebrospinal fluid leaks, and 1 patient had meningitis. Transient diabetes insipidus was diagnosed and treated in 10 patients (6%), whereas permanent diabetes insipidus occurred in 8 patients (4.8%). Panhypopituitarism followed the surgery in 14 patients (8.3%), 13 of whom underwent total hypophysectomy (9 initially and 4 with early reoperations), and in 1 of 10 patients who underwent subtotal hypophysectomy. Nineteen patients (12.8%) who were initially in remission developed recurrent CD after an average of 50 months. The mean follow-up for the 167 patients was 39 months (range 6–157 months). Gamma Knife surgery was the most common modality of radiotherapy used to treat 31 patients (18.5%) who did not achieve remission or later presented with recurrent disease. Bilateral adrenalectomies were performed in 10 patients in the series (6%), 2 of whom developed Nelson’s syndrome. The overall posttreatment remission rate was 95.8%.

**Conclusions.** Even in patients with ideal diagnostic criteria of CD, there remain a significant number of cases in which TSS alone is not adequate to assure long-lasting remission. A multidisciplinary approach is essential to the achievement of satisfactory overall remission rates. (DOI: 10.3171/JNS/2008/109/10/0751)

**Key Words** • Cushing’s disease • microadenoma • pituitary adenoma • transsphenoidal approach

**Cushing’s disease** is one of the most demanding entities to be diagnosed and treated. Even patients with florid CD have a delay of an average of 29 months until the diagnosis is considered.19 Proving that the source of ACTH is from the pituitary region is not a simple process. In spite of high-field-strength MR imaging, the detection rate of pituitary microadenomas can be < 60%.1,3,2,3,36 This is further complicated by the fact that at least 10% of the general population harbors a small pituitary adenoma or a benign cyst, based on MR imaging studies.1,15 Dexamethasone suppression tests have been performed over the years as a method to differentiate pe-
ripheral from central sources of ACTH production. The accuracy of these tests is suboptimal,\textsuperscript{19,29,34} and therefore IPSS has been used as a more reliable test in patients with ACTH-dependent elevation of cortisol to confirm the pituitary source of ACTH overproduction. The accuracy and reliability of IPSS is still debated.\textsuperscript{18,21,41}

The standard treatment for CD is transsphenoidal microsurgical resection.\textsuperscript{19,22,28,32,35–37,39,40} Some factors are recognized as predictors of outcome in CD. Frequently, surgery is recommended based only on laboratory analysis in spite of an apparently normal pituitary on MR imaging.\textsuperscript{22,23,25,36,37} Although remission frequency is obtained in these patients, the remission rate appears lower than in patients with definitive microadenomas. Adults with a classic clinical presentation of Cushing’s syndrome who are harboring a well-defined microadenoma in the pituitary fossa (< 10 mm), as shown on imaging studies and with biochemical studies pointing to the sella turcica as the source of ACTH, form a group of patients in the optimum scenario for the management of this demanding entity. Because outcomes vary for different presentations of CD, we designed this study to verify the remission rate obtained after TSS for this selected group of patients with strong and consistent evidence of an ACTH-producing intrasellar microadenoma.

Methods

A clinical database of patients who presented with CD at the University of Virginia for initial treatment between July 1992 and December 2005 was retrospectively reviewed. To be included in the study, a patient with CD must have presented with an optimum clinical picture. The inclusion criteria were defined as an adult (> 18 years of age) with classic clinical features of CD with MR imaging confirmation.

Diagnostic Criteria

The diagnosis of CD was clinically confirmed, followed by laboratory evidence of hypercortisolemia established in all patients by documenting at least 2 elevated 24-hour UFC levels. Pituitary dependence was established by a variety of means, including high-dose dexamethasone tests and IPSS. The sampling was recommended and performed in cases of Cushing’s syndrome in which noninvasive biochemical investigation, mainly represented by the high-dose dexamethasone test, yielded equivocal findings in confirming the central origin of the ACTH production.

To be included in the study, the patient had to have at least 1 MR imaging study interpreted as showing a microadenoma. Patients < 18 years of age were excluded. Patients with any uncertainty regarding the presence of a microadenoma on the MR imaging study as well as patients with lesions > 10 mm (macroadenomas) in the sella turcica were excluded. Patients who had received any previous treatment for CD (radiation or surgery) were also excluded from the study.

Thus, the selected patients form a homogeneous group of adults presenting classic symptoms of CD, with laboratory data confirming a central source of excess ACTH secretion as well as MR imaging unequivocally demonstrating a pituitary microadenoma. The inclusion and exclusion criteria are given in Table 1.

Surgical Strategy

In all cases, a transsphenoidal approach was performed for resection of the presumed ACTH-secreting pituitary adenoma. The pituitary exploration and the tumor resection were performed by the senior author (E.R.L.) or under his direct supervision. The type of the transsphenoidal approach varied in the series following the evolution of the technique adopted by the surgeons. Initially most of the operations were performed using a sublabial incision. Subsequently endonasal hemitransfixion incision or a direct sphenoidotomy with a posterior septal “push-over” technique was used. More recently we adopted the pure endonasal endoscopic approach. Regardless of the approach, the technique of resection was uniform. After the dural incision, the area of the presumed microadenoma on MR imaging is first explored. Subsequently, the remaining pituitary gland is carefully explored for other possible lesions. All tissue deemed to be abnormal is resected and submitted to the pathology laboratory. Hemihypophysectomy (on the side corresponding to either an MR imaging abnormality or IPSS lateralization), subtotal hypophysectomy, or total hypophysectomy was performed in patients in whom no clearly abnormal tissue could be identified intraoperatively. Total hypophysectomies were generally reserved for very ill elderly patients.

Early reoperation (within 15 days of the initial surgery) was recommended and performed in patients in whom the initial operation was considered a failure, particularly in patients in whom a selective resection or hemihypophysectomy was performed during the initial surgery.\textsuperscript{22} In all patients postoperative serum cortisol levels were measured every 6 hours for 48–72 hours. Surgical remission was considered to have occurred in patients who developed an Addisonian crisis within 72 hours postsurgery and in asymptomatic patients whose serum cortisol levels fell to $\leq 2 \mu g/dl$. Asymptomatic patients whose serum cortisol decreased to normal levels within the initial 72 hours after surgery, with subsequent normalization of 24-hour UFC levels in the postoperative period with or without the need for steroid replacement were also considered in remission.

Specimen Handling and Histological Analysis

All resected tissue was submitted in its entirety to the neuropathologist within minutes of completing the

<table>
<thead>
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<th>TABLE 1</th>
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<tr>
<td>Criteria for inclusion and exclusion for patients with CD who underwent surgery between 1992 and 2005 at the University of Virginia</td>
</tr>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>age</td>
</tr>
<tr>
<td>imaging findings</td>
</tr>
<tr>
<td>condition</td>
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<td>---</td>
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D. M. Prevedello et al.
tumor resection. Specimens were then dissected using a sharp blade, packaged in lens paper, fixed in formalin, and embedded in paraffin for light microscopy. All specimens were initially evaluated using H & E and reticulin staining to identify areas with loss of acinar organization. When a pituitary adenoma was not identified on the initial H & E–stained sections, a “Cushing’s panel” was ordered; this consisted of 30 sequential sections cut through the paraffin block, with every third slide stained with H & E. In sections that showed suspected adenomas, the intervening unstained sections were immunohistochemically stained for reticulin, and for ACTH and other pituitary hormones (prolactin, growth hormone, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, and alpha subunit). If an adenomatous area was not identified, further “Cushing’s panels” were ordered until the tissue block was exhausted.

**Data Collection and Analysis**

For each patient, we documented characteristics (age, sex, duration of CD symptoms, and comorbidities), preoperative laboratory test results (UFC, high-dose dexamethasone tests, and IPSS), preoperative imaging results (based on the surgeon’s preoperative analysis), intraoperative impressions (whether adenomatous tissue was noted by the surgeon and what type of resection was performed), remission status, and postoperative follow-up (number and type of further treatments and time to recurrence, if applicable). Remission on follow-up was defined as normal postoperative 24-hour UFC levels or the need for persistent corticosteroid replacement postoperatively for the duration of follow-up.

**Statistical Analysis**

The chi-square test was performed as a nonparametric statistical analysis. A probability value < 0.05 was considered statistically significant.

**Results**

**Patient Population**

The group considered optimum candidates for treatment of CD comprised 167 patients. Thirty were men (18%) and 137 were women (82%). The mean age was 42.3 years (range 18.2–77 years). All patients had classic signs and symptoms of CD that had been present for an average of 45 months (range 2–244 months). The most common associated symptom was hypertension, which was present in 119 patients (71%). Fifty-nine patients (35%) had headache, and diabetes mellitus was present in 50 patients (30%).

The 24-hour UFC level was definitively elevated in 163 patients (97.6%) in at least 2 samples. The mean UFC was 397 µg/24 hours, varying from 55 to 2900 µg/24 hours (normal range < 50 µg/24 hours). The remaining 4 patients had proven elevated salivary cortisol levels in tests performed at other institutions. Additionally, the mean un suppressed ACTH level was 82.9 pg/ml (normal < 52 pg/ml) varying from 8 to 272 pg/ml, thus reinforcing the probable pituitary origin of the disease. High levels of ACTH and an MR imaging study demonstrating a microadenoma were the only evidence of a central source of ACTH overproduction in 22 patients (13%). Complementary investigation was undertaken in 145 patients (87%) to enhance the diagnosis of CD. One hundred ten patients (66%) underwent either overnight or 2-day high-dose dexamethasone tests. The overnight dexamethasone test was confirmatory (suppression > 90% of the 8 a.m. cortisol level and/or a cortisol level < 5 µg/dl) in 66% of the patients in whom this test was performed. The 2-day high-dose dexamethasone test confirmed a central source of ACTH production (suppression > 90%) in 70% of the patients who underwent this test. Seventy-four patients (44.3%) underwent IPSS, which confirmed a central source of the ACTH overproduction in 72 patients (97%); 2 patients had equivocal IPSS findings. One had a high-dose dexamethasone test supporting a pituitary source of the disease, and the other had elevated levels of ACTH in addition to the MR imaging study demonstrating the microadenoma.

**Surgical Findings**

The endonasal pushover technique was the most common approach used in the series; it was chosen in 78 patients (47%). The endonasal submucosal hemitransfixion route was the second most common variation of the transphenoidal approach; it was used in 48 patients (29%). A sublabial incision was used in 37 patients (22%). A pure endoscopic approach was used in 4 patients (2%). An intraoperative CSF leak occurred in 39 patients (23%), and an autologous fat graft was used to repair the leak. The mean ± standard deviation hospital stay was 3.3 ± 2.4 days (range 1–26 days).

A pituitary adenoma was thought by the surgeon to be present in 148 cases (88.6%), considered suspicious in 8 patients (4.8%), and was unidentified in 11 patients (6.6%). Considering the cases in which the pituitary adenoma was considered definitively present intraoperatively, lateralization of the IPSS was in agreement with the location where the surgeon found the tumor in 70% (44 of 63), whereas the MR imaging was in concordance in 93% of the patients (134 of 144). The fact that the MR imaging was more frequently in congruence with the surgical location of the microadenoma in the sella turcica than the IPSS was statistically significant (p = 0.0001). As represented by the denominators, some patients were not included in this analysis because of lack of data regarding the lateralization of MR imaging and/or IPSS. The correlation between the intraoperative identification of an adenoma and the surgical remission of CD was statistically significant (p = 0.03), as shown in Table 2. Both patients with equivocal results on IPSS had an adenoma clearly identified and confirmed by pathology.

<table>
<thead>
<tr>
<th>Pituitary Adenoma</th>
<th>No Remission</th>
<th>Remission</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>clearly identified</td>
<td>14</td>
<td>134*</td>
<td>148 (88.6)</td>
</tr>
<tr>
<td>suspected or not identified</td>
<td>5</td>
<td>14</td>
<td>19 (11.4)</td>
</tr>
<tr>
<td>total</td>
<td>19</td>
<td>148</td>
<td>167</td>
</tr>
</tbody>
</table>

* Intraoperative identification of an adenoma correlated with remission (p = 0.03).
A selective adenomectomy, typically performed in those cases wherein the adenoma was clearly identified, was performed in 139 patients (83%). Six patients (3.6%) underwent hemihypophysectomies. Ten patients (6%) underwent a subtotal resection of the pituitary gland (subtotal hypophysectomy) with preservation of the superior aspect of the gland attached to the pituitary stalk. A total hypophysectomy was performed in 9 patients (5.4%). The details of resection were not clearly recorded in 3 patients (1.8%). The correlation of the types of resection and surgical remission are shown in Table 3.

**Pathological Findings**

The presence of an ACTH-secreting adenoma was pathologically confirmed in 136 patients (81%). Table 4 summarizes the pathological findings in all 167 patients.

**Initial Postoperative Outcomes**

Postoperative symptoms of hypocortisolism and/or confirmed low levels of serum cortisol were identified in 131 patients (78.4%). The mean serum cortisol in this group was 2.5 µg/dl. Thirty-four patients (20.4%) did not develop addisonian symptoms, and their serum cortisol levels remained elevated. Among the patients who developed hypocortisolemic symptoms, these occurred an average of 38.8 ± 29.1 hours after the surgery. In 2 patients the symptoms or values of serum cortisol could not be evaluated because they had mistakenly received steroids in the perioperative period.

Among the 34 patients who did not present with addisonian symptoms in the postoperative period, 3 (9%) underwent early reoperation, on either the 3rd or the 4th postoperative day. One patient underwent reoperation 90 days after the initial procedure. All 4 patients underwent a total hypophysectomy in the second procedure. In 3 patients a positive ACTH adenoma had been found in their initial specimens, and the pathological findings were again positive for an adenoma in the second procedure in 2 of these patients. No adenoma could be identified in the second specimen of the patient who did not have a positive pathological finding on the initial procedure. One of these 4 patients (25%) with pathological confirmation of an ACTH adenoma subsequently developed hypocortisolemic symptoms and low cortisol levels, confirming remission.

**Endocrinological Outcomes**

Transient diabetes insipidus developed in 10 patients

**Relationship between types of resection performed during surgery and surgical remission**

<table>
<thead>
<tr>
<th>Resection</th>
<th>Remission</th>
</tr>
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<tbody>
<tr>
<td>adenomectomy</td>
<td>126 of 139</td>
</tr>
<tr>
<td>hemihypophysectomy</td>
<td>4 of 6</td>
</tr>
<tr>
<td>total hypophysectomy*</td>
<td>8 of 9</td>
</tr>
<tr>
<td>subtotal hypophysectomy</td>
<td>7 of 10</td>
</tr>
<tr>
<td>total</td>
<td>145 of 164</td>
</tr>
</tbody>
</table>

* Four extra patients not in remission underwent early reoperation with total hypophysectomy, and 1 achieved remission.
† Data not available in 3 patients who achieved remission.

**Complication Rate**

Three patients (1.8%) developed a CSF leak in the postoperative period. All were successfully treated with a single surgical procedure. One of these 3 patients had symptoms of meningitis, successfully treated with antibiotics.
Management of CD in patients with positive MR imaging

**TABLE 5**

<table>
<thead>
<tr>
<th>Pathological Findings</th>
<th>No Remission</th>
<th>Remission</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH adenoma</td>
<td>8</td>
<td>128</td>
<td>136 (81)</td>
</tr>
<tr>
<td>negative</td>
<td>11*</td>
<td>20</td>
<td>31 (19)</td>
</tr>
<tr>
<td>total</td>
<td>19</td>
<td>148</td>
<td>167</td>
</tr>
</tbody>
</table>

* Negative pathological findings correlated with lack of remission (p < 0.0001).

One patient with DVT was treated with implantation of an inferior vena cava filter.

**Analysis of Patients Who Achieved Initial Remission**

**Recurrences.** Among the 148 patients who achieved initial remission, who were followed up for an average of 39 months (range 6–157 months), 19 developed recurrence of CD symptoms (13%). These patients had experienced remission for an average of 50 months (range 12–117 months).

If only the patients followed for longer periods of time are considered, the recurrence rate increased progressively. The recurrence rate rose to 20% for patients followed for more than 12 months (95 patients; mean follow-up 54 months, range 12–157 months). Sixty-nine patients were followed for more than 24 months (range 24–157 months), with a 27% recurrence rate.

Repeat TSS was performed as treatment of recurrent disease in 11 patients (58%); 6 of these patients were treated with TSS alone. Eleven patients underwent GKS for recurrent disease (58%). One patient had conventional radiation therapy (5%), and another had proton-beam radiosurgery (5%). Seven patients had radiation therapy exclusively for treatment of recurrent disease. Five patients received a combination of TSS followed by GKS (4 patients) or conventional radiation therapy (1 patient).

Only 1 patient who had recurrent disease underwent adrenalectomy for disease control after having undergone 3 transsphenoidal operations and radiosurgery (GKS) without control of the disease. This specific patient is currently in remission and has no signs of Nelson’s syndrome.

**Remission Rate.** The overall remission rate at the last follow-up evaluation for these 148 patients who achieved initial remission, including those who had subsequent treatment, was 97.9%. There are 3 patients in this group who did not achieve remission and who are being followed after having radiotherapy or radiosurgery.

**Analysis of Patients Who Did Not Achieve Initial Remission**

Nineteen of the 34 patients who did not achieve initial postoperative remission (including the 3 patients who underwent early reoperation and did not achieve remission) were still having Cushing’s syndrome symptoms and elevated 24-hour UFC levels at follow-up review. The pathological entities encountered among these 19 patients are shown in Table 4. In 11 (57.9%) of the 19 patients an ACTH adenoma was not pathologically proven. None of these patients has been diagnosed with an ectopic source of ACTH secretion. Three of these 19 patients had undergone early transsphenoidal reoperation and total hypophysectomy without success. A second transsphenoidal resection was performed in an additional patient 3 months after the initial procedure. This patient achieved subsequent remission and an ACTH adenoma was pathologically proven. Twelve patients (63.2%) underwent GKS after the unsuccessful initial transsphenoidal resection. Six patients (31.6%) underwent other forms of radiation therapy.

Nine patients without remission (47.4%) had severe manifestations of CD and underwent bilateral adrenalectomies. Seven of these patients had unsuccessfully undergone GKS and 2 had conventional radiation therapy. Two of the 9 patients with adrenalectomies developed Nelson’s syndrome (22%).

Four patients (21%) are still considered to have active CD under medical treatment and anticipating the effects of radiation therapy. Thus, the ultimate remission rate for patients who did not achieve remission after the initial surgical treatment was 79%.

**Overall Analysis**

Table 6 summarizes the overall treatments used and the outcomes in the 167 patients who presented with confirmed CD with a positive MR imaging study showing a microadenoma. Figure 1 demonstrates the management algorithm for CD in these patients.

**Discussion**

**Advantage of a Preoperative Positive MR Imaging Study**

A positive preoperative MR imaging study has clear benefits. Sellar explorations in patients with negative preoperative images increase the risk of deterioration of pituitary function and are associated with a lower remission rate. Conversely, visualization of the lesion on preoperative imaging studies allows a direct approach to the adenoma, and an extra-pseudocapsular dissection can be attempted. The visualization of the lesion preoperatively on MR imaging has been correlated with a higher rate of remission. Salenave et al. divided 54 patients with CD into 2 groups based on the preoperative imaging findings. The majority (52%) had a normal MR imaging study. Intraoperative adenoma identification and confirmatory pathological findings were statistically more common among the patients who underwent TSS alone.
patients with a positive MR imaging study. Nevertheless, there are studies showing that patients with normal (negative) MR images can obtain very satisfactory rates of remission, including the group with preoperative normal MR imaging in Salenave’s study.8,19,33,46

Although ACTH-secreting microadenomas are visible on MR images in 36–63% of cases in patients with CD, false-positive MR images defining a microadenoma may be present in at least 10% of normal patients and should be always considered.15 This fact explains why, for some patients in whom MR images demonstrate an apparent pituitary adenoma, the diagnostic confirmation may still be arduous. As long as the preliminary laboratory data adequately sustain the diagnosis of a central source of ACTH, surgery is indicated. If the initial laboratory data are not consistent, additional studies may be indicated. For this reason, 44% of our patients with positive MR images had further studies to confirm the central source of ACTH by performing IPSS.

The efficacy of the MR imaging in localizing a microadenoma in the sellar area has been stressed.13,28 Invitti et al.19 studied 288 patients with CD and encountered an adenoma in the location corresponding to the MR imaging in 87% of them, whereas the IPSS accurately lateralized the adenoma in 68% of patients. De Herder et al.13 have demonstrated a correct localization of the tumor in 93% of 15 patients with a positive MR imaging study, whereas the IPSS localized the correct side in 73%. Our results are similar; the MR imaging correlated with the location of the adenoma in 93% of the cases and the IPSS in 70%, a difference that was statistically significant (p = 0.0001).

**Surgical Remission Rate**

Transsphenoidal surgery is the most effective treatment for CD. In large series, remission rates have been reported to be between 59 and 90%5,7,9,16,31,33,39,43 Salenave et al.33 reported a 61% surgical remission rate, specifically in patients with a positive MR imaging study. Bochicchio et al.7 analyzed 115 patients with preoperative MR images and found a remission rate of 87.1% in patients in whom the adenoma was identified versus 73.6% in patients with no evidence of tumor. Rees et al.32 reported 100% surgical remission for 23 patients who underwent TSS and who had an MR imaging study showing a microadenoma, versus 69% of 16 patients with normal findings on MR imaging. Because we specifically studied patients with positive MR images, we cannot perform such a direct comparison; however, the outstanding surgical remission rate of 88.6% that we obtained in 167 patients with CD confirms good outcomes for patients who had a preoperative positive MR imaging study.

**Complication Rate**

The incidence of complications after TSS has been correlated with the experience of the surgeon.6,10 Patients who have CD are more prone to systemic complications caused by inherent metabolic and cardiovascular abnormalities associated with the disorder. In particular, perioperative DVT has been reported in ~4% of cases.35 In the present series we had only 1 case (0.6%) of DVT, which was treated with the installation of a vena cava filter. Our incidence of 1.8% for postoperative CSF leaks and 1 case of meningitis (0.6%) are in agreement with other series, in which the reported incidence of CSF leaks after TSS ranged from 1 to 5%, and the incidence of meningitis ranged from 1 to 2%.7,10,14,25 The perioperative mortality rate has been described as ranging from 0 to 2%.7,10,35,40 There were no deaths in our series.

**Postoperative Endocrine Dysfunction**

For CD, independent of preoperative imaging results,
Management of CD in patients with positive MR imaging

the reported rate of new postoperative hypopituitarism ranges from 14 to 89%. Postoperative pituitary deficiency rates have rarely been correlated with the results of preoperative imaging. Rees et al. showed that patients with normal or equivocal findings on preoperative CT or MR imaging had a higher risk of hypothyroidism (81%) than patients with imaging signs of a microadenoma (35%). Salenave et al. demonstrated that hypopituitarism occurred more frequently among patients with normal preoperative MR imaging studies (28%), versus 15% of patients with positive MR images. Indeed, in general, the postoperative pituitary deficiency rate is related to the aggressiveness of surgery. Trainer et al. reported panhypopituitarism in > 80% of patients after radical hypophysectomy, whereas hypothyroidism was found in 10 and 16% of patients, and hypogonadism in 50 and 9% of patients after hemihypophysectomy and microadenomectomy, respectively. The overall loss of any pituitary function in our series was 13.2% (22 patients). Indeed, the aggressiveness of the surgery was directly proportional to loss of pituitary function. All 13 patients (100%) who underwent total hypophysectomy lost anterior pituitary function, whereas only 1 (10%) of 10 patients did so after subtotal hypophysectomy. Among the patients who underwent a less aggressive approach (adenomectomies and hemihypophysectomies), there was no case of panhypopituitarism and only 5.5% lost 1 axis of pituitary function.

Pathological Findings and Surgical Remission

The absence of adenoma on pathological examination has been considered a factor predicting poor prognosis. Remission of CD despite negative results on pathological examination, as occurred in 20 cases in our series, may be explained by postoperative ischemic necrosis of an adenomatous remnant, fortuitous aspiration of a millimetric adenoma during surgery, or a false-negative finding on pathological examination. Our results in patients with CD with no histologically confirmed tumor (remission in 65%) have shown no significant difference from results of larger series of patients undergoing TSS for CD (with or without histological confirmation of a tumor). Remission rates in patients without histological confirmation of tumor resection range from 36 to 69%. Although some authors did not show a significant difference between outcomes of patients in relation to pathological confirmation of an adenoma, in the present series we have demonstrated that the presence of these tumors definitively influences the outcome, because 93.7% of patients with confirmed tumors achieved surgical remission (p = 0.0001). This fact is in agreement with the results of Invitti et al., who found that remission rates were markedly lower in patients in whom an adenoma could not be identified histologically (36 vs 75%, p < 0.01). Similarly, several groups have reported that histological confirmation of adenoma resection is significantly more likely in patients with remission than in patients with persistent disease. Sonino et al. concluded that surgical failure is significantly associated with failure to identify a pituitary adenoma in surgical specimens.

Recurrence Rate

Recurrence rates for CD range between 0 and 26%, with most large studies reporting recurrence rates between 5 and 15%, and a mean time to recurrence of 33–59 months. Although Invitti and colleagues identified significant differences in remission rates related to the histological confirmation of an adenoma, they report no significant difference in recurrence rates related to this factor.

Recurrences have been demonstrated to be less frequent in patients with normal findings on preoperative MR imaging studies than in patients with positive preoperative studies. Salenave et al. reported a 9% recurrence rate among patients in remission in whom findings on previous MR imaging studies had been normal, and 30% among patients with previous positive imaging; however, these findings were without statistical significance. This has been explained by the fact that positive MR imaging studies probably represent a group of patients with larger microadenomas, and consequently tumors would be confirmed more often and the risk of remnant adenomatus cells in the sella turcica would be higher. However, in our series, including only patients with positive preoperative MR images, the recurrence rate has been 12.8% among patients followed for > 14 months, which is compatible with the rates encountered in larger series independent of the findings of the initial MR imaging.

Long-term postoperative surveillance of successfully treated patients with CD is highly recommended and is done by periodic tests for hypercortisolism. The 24-hour UFC was the standard test used to monitor these patients experiencing remission in our series; however, other investigations as such as low-dose dexamethasone and salivary cortisol tests can also be performed. Patients experiencing remission should be assessed annually (or earlier in the presence of recurrent symptoms), and these periodic checkups should be part of the patient’s lifelong care.

Treatment of Patients Who Did Not Achieve Remission

Immediate postoperative assessment of cortisol secretion provides good prognostic information regarding the outcome in patients with CD. Patients whose cortisol levels decrease to < 2–3 pg/dL (55.2–82.8 nmol/L) within 24–72 hours after surgery usually have a sustained clinical and biochemical remission. We have advocated reoperation and more complete hypophysectomy within a few days of the initial surgery in patients whose basal cortisol levels fail to decline satisfactorily. We have analyzed each case in which remission was not achieved within the initial postoperative period. We performed early reoperations for a selected group of 4 patients whom we thought could benefit from early reoperation. Unfortunately, we achieved remission in only 1 of the 4 patients.

The decision on performing reoperations in these patients is very complex. It takes the intraoperative tumor characteristics and pathological findings into consideration. Any dural invasion detected in the specimen or clear cases of cavernous sinus invasion go against any surgical reexploration. The patients’ health and age have also to be considered. Because the second operation tends to be a much more aggressive resection, an important consideration that needs to be undertaken and discussed with young patients is to address the issue of elevated risk of
panhypopituitarism and postoperative infertility. We encourage reexploration in old and ill patients, particularly when the first operation proved the presence of an ACTH-staining pituitary adenoma.

Our preferred treatment for patients who do not achieve remission after TSS is radiosurgery in the form of GKS. We believe that in most cases wherein remission is not obtained, this is a consequence of tumor invasion in the dural membranes around the sella turcica, including the cavernous sinus, so-called ectopic parasellar locations. In most series, GKS resulted in remission in 50–80% of patients with persistent CD. Gamma Knife surgery, however, offers some advantages over conventional radiotherapy and repeat TSS. Relative to conventional radiotherapy, GKS allows delivery of highly focused radiation to the sellar region while sparing surrounding critical structures. When treatment directed at the sella turcica fails, bilateral adrenalectomy is highly effective in controlling hypercortisolism.

The widespread availability of laparoscopic adrenal surgery and new techniques such as the posterior retroperitoneoscopic adrenalectomy have now made bilateral adrenalectomy an attractive choice in patients with CD in whom pituitary surgery has failed. This procedure is well tolerated, with very little morbidity, and nearly a 100% cure rate is attained in patients with ACTH-dependent hypercortisolism. The development of Nelson’s syndrome is always a concern in these patients, but with periodic MR imaging of the pituitary and measurement of basal ACTH, the potential for development of Nelson’s syndrome is low, particularly after sellar radiation. Because of the significant increase in morbidity and mortality rates in patients with untreated CD, we generally advise laparoscopic bilateral adrenalectomy in patients with significant hypercortisolism in whom surgery and radiosurgery have failed. In our series we have performed 10 adrenalectomies, and 2 of these patients (20%) developed Nelson’s syndrome. The risk of Nelson’s syndrome following bilateral adrenalectomy has been reported to be 20–35%. 17,20,24,39

Conclusions

Even in patients with a favorable scenario in CD, there remains a significant number of cases in which TSS is not adequate to produce permanent relief of symptoms. Because late recurrences occur, long-term postoperative surveillance of successfully treated patients with CD is extremely important. A multidisciplinary approach is necessary in diagnosis and therapy to achieve satisfactory overall remission rates in CD.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Address correspondence to: Edward R. Laws Jr., M.D., Department of Neurosurgery, Brigham & Women’s Hospital, PBB3, 15 Francis Street, Boston, Massachusetts 02115. elaws@partners.org.