Transsphenoidal surgery in Cushing disease: 10 years of experience in 34 consecutive cases

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Objective. Cushing disease is a rare disorder. Because of their small size the adrenocorticotropic hormone (ACTH)-producing tumors are often not detectable on neuroimaging studies. To obtain a cure with transsphenoidal surgery (TSS) may therefore be difficult. In this report the authors present 10 years of experience in the treatment of patients with Cushing disease who were followed up with the same protocol and treated by the same surgeon.

Methods. Thirty-four patients, 26 of them female and eight of them male (mean age 40 years, range 13–74 years) were studied. All had obvious clinical signs and symptoms of Cushing syndrome. Magnetic resonance (MR) imaging was performed in all patients, and inferior petrosal sinus (IPS) sampling was done in 14.

In 12 patients MR imaging indicated a pituitary tumor; 10 were microadenomas and two were macroadenomas. In six patients with no visible tumor, the results of IPS sampling supported the diagnosis. All patients underwent TSS; the mean follow-up duration was 6 ± 0.5 years. Selective adenomectomy was performed in 32 and hemihypophysectomy in the other two patients. A cure was obtained in 31 patients (91%) after one TSS and in two more patients after further TSS; one patient was not cured despite two TSSs and one underwent bilateral adrenalectomy. Disease recurrence was seen in two patients after 3 years, and they were successfully treated with stereotactic gamma knife surgery. Half of the patients had an ACTH deficiency postoperatively, whereas one third had other pituitary hormone insufficiencies. There were no serious complications attributable to the surgical intervention.

Conclusions. Transsphenoidal surgery with selective adenomectomy is an effective and safe treatment for Cushing disease. In the patients presented in this study, the surgical outcome seemed to depend on careful preoperative evaluation and the surgeon’s experience. For optimal results in this rare disease the authors therefore suggest that the endocrinological, radiological, and surgical procedures be coordinated in a specialized center.

Key Words • Cushing disease • transsphenoidal surgery • outcome

Cushing disease is a rare disorder with an incidence of 1.2 to 1.7 cases/million/year.14 Transsphenoidal surgery of the ACTH-producing pituitary adenoma is the treatment of choice,13,17 with reported remission rates of between 64 and 93%.2,9,10,15,25,27,28 Compared with patients who have other pituitary tumors, those with hypercortisolism have higher pre- and postoperative morbidity and mortality rates, including an increased risk of thromboembolism, hemorrhage, and infections, all of which necessitate qualified and careful pre-, peri-, and postoperative management. With this in mind we present a retrospective study of 34 patients with Cushing disease who were treated with TSS during a 10-year period by one surgeon, focusing on factors that may have determined the surgical outcome.

Clinical Material and Methods

Patient Selection

Between 1990 and 1999, 36 consecutive patients with Cushing disease were diagnosed at the Department of Endocrinology and Diabetology, Karolinska Hospital, Stockholm, Sweden. During this period all patients with Cushing disease were evaluated using a similar protocol and were surgically treated by the same pituitary surgeon (A.Ä.). Two of the 36 patients were not included in this study for the following reasons: one patient died of a pulmonary embolism before surgery, and one was surgically treated but excluded because of an ACTH-producing pituitary tumor from which intracerebral metastases arose. Thus, 34 patients were included, 26 female and eight male patients with a mean age of 40 years (range 13–74 years, Table 1). The duration of signs and symptoms before diagnosis varied from 6 months to 10 years (mean 3.1 years). All patients had clinically obvious Cushing syndrome. None of the patients received cortisol-lowering medication preoperatively.

Preoperative Characteristics

In 12 patients (35%) MR imaging of the pituitary area demonstrated a tumor; 10 of these were microadenomas and two were macroadenomas. We performed IPS sampling in 14 patients: in eight patients in whom a tumor was demonstrated or suspected on MR imaging, the results of IPS sampling confirmed this. In six patients with no visible tumor on MR images, the results of IPS sampling supported the diagnosis of an ACTH-secreting pituitary adenoma.
Preoperative Evaluation

The preoperative biochemical investigations to confirm Cushing disease consisted of assessment of circadian levels of serum cortisol and ACTH, and 24-hour urinary cortisol and overnight dexamethasone suppression tests (1 mg oral dexamethasone administered between 10 and 11 p.m.) on Day 1, with measurement of the serum cortisol level at 8 a.m. on Day 2. To confirm pituitary dependency, low- and high-dose dexamethasone suppression tests were performed when needed.

All patients underwent MR imaging of the pituitary and hypothalamic regions, including imaging with Gd contrast enhancement (1.5-tesla magnet). The IPS sampling method was introduced at our hospital in 1994, and results of this examination were available in 14 patients. During IPS sampling, 100 μg corticotropin-releasing hormone was injected intravenously, and ACTH was measured in a peripheral vein and in the left and right petrosal sinus before and 2 and 5 minutes after this injection. A ratio of 1.4 between the two sides was used for side localization.13

Surgical Procedures

Surgery was the primary therapy, and all 34 patients were surgically treated via a sublabial transseptal approach. When needed, further exposure was obtained by widening the piriform aperture to visualize the lateral parts of the sellar region. A cross incision of the outer and inner layer of the dura mater was made and the inner layer was meticulously dissected from the pituitary capsule to obtain a clear-cut dissection plane of the pituitary gland from the cavernous sinus (Fig. 1) on each side and from the floor of the sella turcica. This was done to obtain a dissection plane that would facilitate a later complete removal of pituitary tissue in the area. When MR imaging failed to demonstrate a definitive tumor, the entire pituitary gland was explored through a horizontal incision made between the upper and lower half of the structure. The lower part was then removed piecemeal. The neurohypophysis was regularly identified from below and separated from the adenomatous tissue to save ADH function. In the patients in whom the result of IPS sampling was available, the side indicated was explored first through a vertical incision made close to the midline.

Hydrocortisone cover was given during surgery, followed by replacement with cortisol acetate postoperatively, and 5000 IU heparin was given daily preoperatively and 1 week postoperatively. The adenoma tissue was examined microscopically and with immunohistochemical methods.

Postoperative Evaluation

The patients were followed up in accordance with conventional criteria. Clinical evaluation and reassessment of circadian levels of cortisol and ACTH, 24-hour urinary cortisol measures, and overnight dexamethasone suppression tests were performed 8 to 12 weeks postsurgery. Examinations were then performed every 6 months until the patient’s condition stabilized and annually thereafter.

Long-term cure was defined as clinical remission, normal or low serum cortisol and plasma ACTH levels, and normal or subnormal 24-hour urinary cortisol levels, as well as serum cortisol values below 100 nmol/L on Day 2 of the overnight dexamethasone suppression test. Residual pituitary function was assessed at the aforementioned intervals, whereas the first postoperative MR image was obtained after 3 to 6 months.

Hormone Assays

Cortisol levels in urine and serum, PRL, GH, LH, FSH, estradiol, testosterone, TSH, T3, T4, and plasma ACTH were measured using routine commercially available methods. Insulin-like growth factor–I levels were determined in serum by radioimmunoassay after acid ethanol extraction,1 and the values were related to a normal cohort of 448 individuals ages 20 to 96 years.31

Results

Postoperative Outcome

In 32 patients a selective adenomectomy was performed,
and in another two a hemihypophysectomy was chosen, in one of them because the adenoma extended down into the bone of the clivus. Most tumors that were not seen on MR imaging were small and difficult to find at surgery. A cure was accomplished in 31 patients after TSS. Immunohistochemical findings for ACTH in the adenoma were positive in 24 patients (71%).

Three patients who underwent TSS were not cured and underwent a second operation. The immunohistochemical findings were negative for ACTH in all three. In one patient selective adenomectomy was performed, and the other two underwent hemihypophysectomy; two were subsequently cured. One of them had received external radiation therapy (50 Gy) preoperatively. The third patient underwent bilateral adrenalectomy after two transsphenoidal operations and GKS thereafter, but the ACTH levels were still elevated.

Tumor recurrence was seen in two patients, in both cases after 3 years. At the first postoperative evaluation, these two patients had normal levels of serum cortisol and ACTH. At recurrence they were treated successfully with GKS. Thus, a cure was obtained in 31 (91%) of 34 patients after one transsphenoidal surgical intervention (Table 2). Taking into account recurrences and repeated treatment, 33 (97%) of 34 patients were cured.

The mean follow-up duration was 6 ± 0.5 years (range 1–12 years) after surgery. The percentage of the 31 patients who were cured per 1-year interval of follow up after one transsphenoidal operation is shown in Fig. 2.

We also compared the results of IPS sampling with the surgical and immunohistochemical findings. In nine patients with positive results on IPS sampling the adenoma was difficult to identify at surgery; in seven of these IPS sampling was helpful, but it was misleading in two. In 13 of 14 patients immunohistochemical staining was positive for ACTH.

Postoperative Complications

All patients were treated with antibiotic drugs and heparin preoperatively and 1 week postoperatively. None experienced meningitis or encephalitis, and no bleeding events occurred. There were no deaths related to surgery, but one patient died of renal insufficiency 4 years postoperatively. Vision and visual fields were not affected preoperatively or by the surgery. In one patient a retinal venous thrombosis developed in one eye at 1 month postoperatively that had no obvious connection to the surgical intervention.

Evaluation of Hormone Levels

Preoperative and postoperative pituitary function values are given in Tables 1 and 2. Postoperative recovery time for the hypothalamic-pituitary-adrenal axis and discontinuation of glucocorticoid replacement treatment was between 1 and 3 years (mean 1.5 years) in 17 patients, whereas 17 patients still have an ACTH deficiency and require glucocorticoid replacement.

Hypogonadism was the most common preoperative deficiency seen in 17 patients (13 female patients), and the FSH/LH function remained insufficient in six of them postoperatively. Hypothyroidism was seen in two patients preoperatively and in both of these and one additional patient postoperatively. Preoperative GH insufficiency was seen in two patients, and resolved in both cases. In four other patients GH insufficiency developed postoperatively; none of these patients had diabetes insipidus preoperatively. Postoperatively, ADH insufficiency was seen in two patients, but only one of them had a permanent dysfunction. In summary, six patients had one pituitary insufficiency, three patients had two insufficiencies, and one had three insufficiencies postoperatively. In one of 18 patients PRL was elevated preoperatively (34 μg/L) and remained elevated postoperatively (54 μg/L). This patient was cured, however, of her Cushing disease. In total, one third of our patients experienced pituitary insufficiency other than for the hypothalamic-pituitary-adrenal axis postoperatively (Table 2).

Discussion

In our patients the cure rate after primary selective pituitary adenomectomy for Cushing disease was 91% after a mean follow up of 6 years. Previous studies have shown initial cure rates after TSS of 64 to 93%, decreasing to between 50 and 80% in a longer perspective of time.

Several factors are important in the endeavor to obtain satisfactory results. Preoperative identification of the ACTH-producing pituitary adenoma is important both for the surgical outcome, avoidance of complications, and the possibility of curing the patient. In our study only two pa-
Ten years’ experience with microsurgery to treat Cushing disease

Patients had macroadenomas, whereas 32 had microadenomas, of which 22 (69%) were not visible on MR images. Sampling in the IPS was only performed in 14 patients, in whom a suspected microtumor was confirmed in eight cases. It has been recommended that IPS be reserved for assessment of patients with Cushing disease when MR imaging is inconclusive, to distinguish ectopic from pituitary ACTH secretion. Many ACTH-producing adenomas are invisible on MR imaging, but unfortunately the accuracy of lateralization afforded by IPS sampling is only 50 to 60%. Thus, IPS sampling, although it is extremely helpful in excluding the possibility of ectopic ACTH production, is not very helpful in localizing the pituitary tumor; therefore, we emphasize the need for the surgeon to examine the entire gland. Although imaging modalities are improving, identification of the tumor still depends on the surgeon’s skill and experience. In our study most of the adenomas seem to have been correctly identified before or during surgery, as judged from outcome and the pathology report.

A low serum cortisol level is the expected response to successful pituitary surgery, but the time to recovery of normal ACTH-producing cells is highly variable, ranging from months to 2 to 3 years. An earlier study has shown that the longer the need for glucocorticoid substitution remains, the higher the probability that the patient will remain free of recurrent disease in the long term. In our patients a chronic adrenal insufficiency developed in half of them postoperatively, whereas the other half were able to discontinue the steroid replacement therapy after a mean of 1.5 years. It can be argued that the postoperative treatment with cortisone acetate might keep suppressing the normal ACTH-producing cells through negative feedback, resulting in subnormal cortisol secretion. The effect of cortisone acetate on the pituitary in the long term becomes more difficult to evaluate. In our experience, recovery of adrenocortical function is seen up to several years postoperatively, making repeated tests for endogenous cortisol necessary.

Avoidance of other pituitary insufficiencies besides ACTH after TSS is of great importance because of the increased incidence of morbidity and mortality. Epidemiological data indicate that adults with hypopituitarism have a reduced life expectancy compared with healthy controls, with a greater than twofold increase in deaths from cardiovascular diseases. Most likely the reason for the preoperative insufficiencies of the FSH–LH, TSH, and GH axes in patients with ACTH-producing adenomas is the well-known suppressive effect of hypercortisolism on these axes. In our study hypothyroidism and hypogonadism did not resolve after surgery in three and six patients, respectively, despite their being cured of hypercortisolism. In these cases it cannot be firmly established whether the insufficiencies were due to pre-, peri-, or postoperative events. In one patient permanent diabetes insipidus developed; GH insufficiency developed in four. None of our patients experienced panhypopituitarism. The frequency of postoperative hypopituitarism has varied widely in previous reports. Hypothyroidism and hypogonadism ranged from less than 2% to 27 to 48%, whereas transient diabetes insipidus was seen in 48%, and permanent diabetes insipidus in 25%. Our patients underwent selective adenomectomy, and the number of patients with postoperative pituitary insufficiencies (other than ACTH) were few. These results might therefore indicate that a selective resection of an ACTH-secreting tumor is a favorable factor in minimizing the risk of insufficiencies.

Recurrent and persistent Cushing disease results from residual tumor tissue, and it is well known that the number of recurrences increases with time. Early identification of patients at risk for recurrences and relapse would be attractive. Chen, et al., have shown in their large series of 174 patients with Cushing disease that those with morning cortisol concentrations lower than 3 μg/dl (83 nmol/L) on postoperative Day 3 (after an overnight dexamethasone suppression test) had a 93% chance of remission at the 5-year follow-up examination. This outcome has also been extensively reviewed by Oldfield, et al.

In our study two patients whose disease was in remission suffered relapses after 3 years; these two patients were successfully treated with GKS. We and other investigators have shown that this treatment modality is an effective option when microsurgery fails to cure the patient, if the residual tumor is visible, and the distance to the optic chiasm is a minimum of 2 mm. Dickerman and Oldfield have shown that the residual tumor can be found at or near the site at which the lesion originally appeared. Thus, the surgeon’s knowledge of the location where the extent of the operation might be incomplete can be very helpful in deciding if GKS would be an option.

Thromboembolic complications are common in Cushing disease, and undergoing TSS further increases the risk. In a study by Boscaro, et al., it was shown that prophylactic anticoagulation reversed the prothromboembolic state and avoided postoperative thromboembolic events. This is in accordance with results reported in previous studies. Our patients were treated with heparin injections preoperatively and 1 week postoperatively without complications, leading us to advocate the use of heparin perioperatively in patients with Cushing disease.

Conclusions

We have found that TSS with selective adenomectomy is an effective and safe treatment for patients with Cushing disease. In our center the number of hypophysectomies are on average 50 per year, which seems to be adequate to obtain skill and experience even in treating a rare entity like Cushing disease. Thus, our results favor coordination of endocrinological, radiological, and surgical procedures in specialized centers to accumulate sufficient experience with this rare disease and optimize surgical outcome.

References


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