Complications in a contemporary series of patients who underwent transsphenoidal surgery for Cushing's disease

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Object. Transsphenoidal surgery is the usual treatment of choice for adrenocorticotrophic hormone-secreting pituitary adenomas associated with Cushing's disease. In this paper the authors investigate the complications of transsphenoidal surgery in the treatment of a contemporary series of patients with Cushing's disease.

Methods. Between January 1992 and December 1997, 105 patients with Cushing's disease underwent transsphenoidal surgery at the University of Virginia Health Sciences Center. A retrospective analysis of the complications was conducted, and the mortality rate was found to be 0.9% and permanent morbidity was 1.8%. The overall number of complications was 14 (13.3%), which included seven complications directly related to surgery; one instance of permanent diabetes insipidus; one syndrome of inappropriate secretion of antidiuretic hormone; and five medical complications (four patients developed deep vein thrombosis and one developed pneumonia).

Conclusions. Transsphenoidal surgery for Cushing's disease has a higher complication rate than that for pituitary adenomas in general. This is primarily related to a greater number of medical complications, most notably deep vein thrombosis, resulting from the generally debilitated state of most patients with Cushing's disease. In view of the high incidence of deep vein thrombosis in these patients, prophylaxis for thromboembolism during the perioperative period is recommended.

Key Words * Cushing's disease * transsphenoidal surgery * complications * deep vein thrombosis

Over the last three decades, transsphenoidal surgery has become established as the primary therapy of choice for Cushing's disease.[2,3,12,13,15] Although it has potentially serious complications, in the hands of experienced surgeons it is a safe procedure with a mortality rate of less than 1%.[3,6,11] Patients with Cushing's disease often have associated medical problems such as obesity, hypertension, and diabetes that increase the risk associated with surgery. However, because most of these patients are relatively young and their pituitary tumors are usually small, it is somewhat less likely that they will suffer from complications of the surgery itself.[12] The aim of this study was to determine whether complications from transsphenoidal surgery in patients with Cushing's disease were comparable to those in more generalized series of patients treated for pituitary adenomas of all types.

CLINICAL MATERIAL AND METHODS

At the University of Virginia Health Sciences Center between January 1992 and December 1997, 105 consecutive patients with Cushing's disease underwent surgery via the transsphenoidal route. There were 22 male and 83 female patients, whose mean age was 38.5 years (range 6-78 years). Central adrenocorticotrophic hormone-dependent Cushing's disease was diagnosed using endocrinological function tests in all patients, and if the tests had been performed at another institution the results were verified by the endocrinologists at the University of Virginia Health Sciences Center. Twenty-seven patients had recurrent disease for which they had previously undergone surgery: 21 elsewhere and six at our institution. Magnetic resonance (MR) imaging of the pituitary fossa was performed in all cases. Preoperative diagnoses were in 74 patients with microadenomas and 13 with macroadenomas; 18 had normal imaging studies (Table 1).

TABLE 1 CHARACTERISTICS OF PATIENTS UNDERGOING TRANSSPHEROIDAL SURGERY FOR CUSHING'S DISEASE	
Characteristic	No. of Patients
total	105
gender	
male	22
female	83
mean age (yrs)	38.5
range	6-78
presumed microadenomas (18 w/ normal MRI)	92
presumed macroadenoma	13
primary ops	
microadenoma	72
macroadenoma	6
secondary op	
microadenoma	20
macroadenoma	7
complications	14 (13.3%)

A single surgeon (E.L.) performed each surgery by using the sublabial or endonasal route. Nafcillin or vancomycin were administered prophylactically during the operative procedure. Elastic stockings were utilized intraoperatively and throughout the patients' hospital stay. Pneumatic compression devices were not used, nor were low-dose heparin therapy or routine lower-extremity vascular Doppler studies. Later in the series, patients with Cushing's disease were started on aspirin therapy (81 mg/day) on the 1st postoperative day.

The patients were monitored postoperatively by using clinical and biochemical methods, with particular attention to fluid balance. A routine noncontrast-enhanced computerized tomography (CT) scan was obtained the day after surgery, and the nasal packing was removed 12 to 48 hours postsurgery. Hydrocortisone therapy was not given during or after surgery; however, if patients developed signs and symptoms of adrenal insufficiency and had a serum cortisol level of less than 3 µg/dl they received maintenance hydrocortisone replacement therapy. Patients with no complications were discharged on the 3rd day postsurgery and received follow-up care in our pituitary clinic. Most patients in whom remission of disease was achieved required hydrocortisone therapy for many months.

A retrospective analysis of the patients was conducted. Criteria for remission of Cushing's disease in the

immediate postoperative period included a decrease in cortisol levels to subnormal amounts and the need for cortisol replacement therapy (Table 2).

TABLE 2		
REMISSION OF CUSHING'S DISEASE AFTER TRANSSPHENOIDAL SURGERY IN 105 PATIENTS		
Group	No. of Cases	Percentage
patients overall	79 of 105	75.2
primary ops for microadenoma	64 of 72	88.9
macroadenomas & reops	15 of 33	45.5

RESULTS

As shown in Table 3, 14 patients (13.3%) developed a complication, and one patient died (0.9%). The average age of the patients with complications was 39.9 years, and the ratio of women to men was 3.4:1, which is similar to the overall series of patients with Cushing's disease. Only one of the patients who developed a complication had undergone previous transsphenoidal surgery, and the patient who died had previously been treated medically and with gamma knife radiosurgery. According to neuroradiological findings, five patients who developed a complication had microadenomas, four had macroadenomas, and five had normal MR images.

TABLE 3					
COMPLICATIONS IN A CONTEMPORARY SERIES OF TRANSSPHENOIDAL SURGERY FOR CUSHING'S DISEASE*					
Case No.	Age (yrs), Sex	Previous Treatment	MRI Findings	Inva-sion	Complication
1	24, F	—	micro	no	permanent DI
2	48, M	trans†	macro	no	nasal septal perforation
3	52, F	—	macro	yes	deep vein thrombosis
4	32, F	—	micro	yes	CSF rhinorrhea (postop)
5	52, M	—	normal	no	deep vein thrombosis
6	37, F	—	normal	no	ocular neuropathy
7	53, M	—	micro	yes	deep vein thrombosis
8	68, F	Gk†	normal‡	no	SIADH, hyponatremia (fatal)
9	71, F	—	micro	—	pneumonia & UTI
10	36, F	—	macro	yes	deep vein thrombosis
11	28, F	—	micro	no	epistaxis
12	45, F	—	macro	yes	3rd cranial nerve palsy (transient)
13	32, F	—	normal	no	nasal septal perforation
14	47, M	—	normal	no	wound dehiscence
* All adenomas presumed from MR findings were confirmed on pathological examination, except in Case 9. Abbreviations: Gk = Gamma knife; invasion = invasion of dura seen on pathological examination; macro = macroadenoma; micro = microadenoma; trans = transsphenoidal; UTI = urinary tract infection; — = none.					
† These procedures were performed at another institution.					
‡ Normal pituitary gland according to pathological examination.					

Fluid Homeostasis

Diabetes insipidus (DI) developed postoperatively in 10 patients. Seven cases of DI developed in the first

48 hours postoperatively, were transient in nature, and were corrected by a single dose of desmopressin. Two patients developed delayed DI, at 2 weeks and 1 month postoperatively, respectively. Their DI was transient in nature and required a short course of desmopressin. We did not regard these cases as complications. Delayed onset, permanent DI requiring hormone replacement therapy occurred in one patient 2 months postoperatively.

Six patients developed hyponatremia in this series; in five cases it occurred during the immediate postoperative period (48 hours) and was transient, resolving after fluid intake was restricted. These patients were not included in the group with complications. Symptomatic hyponatremia occurred 2 months postoperatively in one elderly patient who had presented at another institution with obtundation and a serum sodium level of 107 mg/dl; she showed no signs of meningitis. She developed fatal central pontine myelinolysis after rapid correction of her hyponatremia and was the sole death in this series. It is possible that delayed syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and cortisol deficiency played a role in her death. There was no evidence of delayed cerebrospinal fluid (CSF) rhinorrhea, pneumocephalus, or meningitis.

Complications Related to Surgery

Seven patients had complications specifically related to the surgical procedure. In one patient, permanent unilateral ocular neuropathy with no subsequent visual improvement occurred as a result of a misdirected approach. The postoperative CT scan did not reveal a fracture of the optic canal and the injury was presumed to be related to direct contusion of the optic nerve or vasospasm. In another patient, early reoperation and packing of the sphenoid sinus with fat was used to control postoperative CSF rhinorrhea. One patient with a macroadenoma developed a transient third cranial nerve palsy, presumably related to removal of tumor from the cavernous sinus. A CT scan demonstrated no intracranial disease and the third cranial nerve function returned to normal during the following 3 days. Epistaxis occurred 3 weeks after surgery in a single patient, requiring cauterization of the sphenopalatine artery. There were two patients with nasal septal perforations seen on postoperative follow-up images, but both were asymptomatic. These patients had mucosal tears noted at the time of surgery, and an attempt was made to repair these tears during closure; neither of these patients had overt diabetes mellitus. Finally, dehiscence of the abdominal fat graft site developed in one patient.

Nonsurgery-Specific Complications

Deep vein thrombosis occurred in four patients between 2 weeks and 1 month postsurgery. Greenfield filters were placed in two patients, and all four were successfully managed with coumadin therapy. No pulmonary embolus occurred.

Pulmonary and urinary tract infections requiring intravenously administered antibiotic drugs occurred in an elderly patient 1 week postsurgery.

Remission of Cushing's Disease

The entire series of 105 patients included 27 patients who underwent reoperation and a number of patients who had deviations from the ideal preoperative laboratory values, which led to a diagnosis of adrenocorticotrophic hormone-dependent Cushing's disease. These results are partially due to the status of our practice as a referral center for difficult cases. In the immediate postoperative period, disease in 79 patients (75.2%) was in remission and in 26 (24.8%) it was not. If the 27 secondary procedures and the 16 macroadenomas (seven also included in secondary procedures and six in primary) are considered

separately because of anticipated suboptimal results, a remission rate of 88.9% was achieved in the 72 remaining patients who underwent primary surgery for microadenomas.

DISCUSSION

Transsphenoidal surgery for the treatment of pituitary tumors is a safe procedure in experienced hands.[1-3,11,13,14,23] The surgical mortality rate ranges from 0.4 to 2%.[3,11-14,17,22] and the single death in our series (0.9%) is in keeping with this. The overall complication rate for transsphenoidal surgery accompanying pituitary adenomas is 3.3 to 9.3%.[2,3,14,17,19] and in this series it was 13.3%, indicating that patients with Cushing's disease have a higher risk of complications than those with other pituitary adenomas.[6] However, if only the permanent complications are included, namely the patients with permanent DI and ocular neuropathy, then the rate is 1.8%. The size of the tumor and previous surgery have been described as risk factors[3,13] in transsphenoidal surgery. In this series, however, only one of 27 patients who had previously undergone transsphenoidal surgery developed a complication. There was an increased incidence of complications in patients with macroadenomas (four of 13) or with normal MR images (four of 18), as compared with those patients with microadenomas (five of 74).

Complications in This Series

Diabetes Insipidus. Postoperatively, DI may be transient or permanent but only the permanent type is regarded as a complication, and it is rare, with a reported incidence of 0.5 to 15%.[2,11] In this series it was 0.95%. Transient DI occurs in 10 to 60% of reported cases and it occurred in 8.5% of our patients. Transient polyuria is frequently noted during the 1st postoperative day, and usually only 20% of patients require treatment with desmopressin.[9] Early transient DI is thought to be caused by temporary dysfunction of vasopressin-producing neurons as a result of surgical trauma.[9]

Syndrome of Inappropriate Secretion of Antidiuretic Hormone. Typically, SIADH occurs 5 to 7 days postsurgery. One of the explanations for this phenomenon has been the release of stored ADH from the damaged posterior pituitary nerve terminals.[3,4,9,10,20,24] In our series, the hyponatremia usually was transient and occurred in the first 2 days postsurgery in five cases, and 2 months later in one case. The very early postoperative hyponatremia is probably not SIADH, but is likely related to overhydration and hemodilution in the perioperative period.

Vascular Injury. Vascular injury occurring during transsphenoidal surgery is a rare yet potentially fatal complication and includes carotid artery (CA) rupture, CA cavernous fistulas, traumatic aneurysms, subarachnoid hemorrhage, CA vasospasm, and stroke.[2,3,11-13,16,17,19,21] Postoperative hemorrhage from the cavernous sinus, CA, or tumor bed can occur, causing visual deterioration or hypothalamic injury. Incidence of injury varies from 0.4 to 1.4%.[3] and there were no vascular injuries in this series.

Visual Complications. Optic nerve injury occurred in one patient in our series, and was thought to be caused by a misdirected approach and contusion of the optic nerve. The patient was treated with high-dose steroids, and the possibility of a fracture of the optic canal was excluded on CT scanning. Other possible causes of injury include vasospasm, a postoperative hematoma, or devascularization of the optic apparatus.[1] Delayed visual deterioration can also occur with the empty sella syndrome.[2]

Cranial Nerve Injuries. Injuries to the cranial nerves (excluding the second cranial nerve) usually occur as a result of exploration of the cavernous sinus for tumor, and the nerve most commonly injured is the sixth cranial nerve.[3,13,17] The reported incidence is 0.4 to 1.9% and the injury may be temporary or permanent.[3] The single patient in our series who developed a transient third cranial nerve palsy was

thought to have developed the complication as a result of our surgical exploration of the cavernous sinus.

Meningitis and CSF Leaks. A CSF leak may occur intra- or postoperatively and entails the risk of meningitis, which is a potentially fatal complication.[6,11] The reported incidence of CSF fistulas after transsphenoidal surgery is 1 to 4% and the incidence of meningitis is 0.8 to 2%. A CSF leak that is recognized intraoperatively can be repaired by packing the sella and the sphenoid sinus with fat or muscle.[17] Meningitis may also occur without a postoperative CSF leak. Although a small percentage of these will resolve spontaneously, many will require operative repair,[12] as was the case in the patient in our series who developed a postoperative CSF leak. Prophylactic antibiotic drugs are used by most surgeons in an attempt to prevent meningitis but the effectiveness of these prophylactic medications has never been proven.[5,7,12,15,25]

Nasal Complications. Problems related to the nasal aspects of the operation are rarely fatal but may produce significant discomfort and distress, and include sinusitis (1-15%), septal perforations (0.3-0%), and epistaxis (0.4-4.3%).[2,3,12,17] Nasal septal perforation can lead to chronic infection and may require secondary surgical repair. Nasal tip deformities or a saddle nose may occur when the nasal spine or cartilage is too aggressively removed. Postoperative sinusitis may require additional medical or surgical treatment. The two patients with nasal septal perforation in this series were asymptomatic, and these complications were not clearly related to operative techniques. Epistaxis occurred in one of our patients 3 weeks postsurgery and required cauterization of the sphenopalatine artery. Epistaxis can be treated with nasal packing, cautery, or ligation/embolization of the internal maxillary artery.[2,3]

Medical Complications. Deep venous thrombosis and pulmonary emboli have been reported to occur with varying frequency after transsphenoidal surgery.[2,3,6] Fahlbusch, et al.,[6] reported four cases of deep venous thrombosis and pulmonary emboli in their series of 101 patients who underwent transsphenoidal operations for Cushing's disease. The two operative deaths in the report published by Ciric, et al.,[3] were caused by pulmonary emboli. In our series, four patients (3.8%) developed deep vein thrombosis between 2 and 4 weeks postsurgery.[3] None developed a pulmonary embolus. We postulate that the obesity associated with Cushing's disease and the consequent relative immobility of these patients, together with the hypercoagulable state postsurgery may be responsible for the relatively high incidence of deep vein thrombosis in patients with Cushing's disease. Our standard procedure had been to use elastic stockings and early mobilization to prevent these complications. We have since developed a policy of administering postoperative aspirin therapy to patients with Cushing's disease.

Pneumonia was the cause of death in two patients treated for Cushing's disease by Fahlbusch, et al.[6] There was one patient in our series who developed pneumonia and a urinary tract infection requiring hospitalization and medical treatment. One patient had dehiscence of the abdominal fat graft wound; poor healing is characteristic of the hypercortisolemic state. Patients with Cushing's disease are frequently debilitated because of associated medical conditions such as obesity, hypertension, and diabetes mellitus, which render them more susceptible to infections in the postoperative period.

CONCLUSIONS

Transsphenoidal surgery remains a safe procedure for the treatment of patients with Cushing's disease. The surgical complications and mortality rates are comparable to those found in more general series of patients undergoing transsphenoidal surgery for pituitary adenomas. In our series the complication rate (13.3%) is higher than those in other published series of transsphenoidal microsurgery for pituitary adenomas in general (3.5-9.3%),[2,3,12,18,23] although the incidence of serious complications causing

permanent morbidity is low (1.8%). We believe that this elevation of the complication rate in our series is related to the increased occurrence of medical problems, namely deep vein thrombosis (and the life-threatening risk of pulmonary embolus), pneumonia, and poor wound healing in patients with Cushing's disease. Because there is a definite risk of deep vein thrombosis that can be life threatening in these patients, we believe that they should undergo prophylactic therapy for this complication during the perioperative period.[8]

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Manuscript received June 8, 1998.

Accepted in final form March 29, 1999.

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