Complications after transsphenoidal surgery for patients with Cushing's disease and silent corticotroph adenomas

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OBJECT The purpose of this study was to describe complications associated with the endonasal, transsphenoidal approach for the treatment of adrenocorticotrophic hormone (ACTH)–positive staining tumors (Cushing's disease [CD] and silent corticotroph adenomas [SCAs]) performed by 1 surgeon at a high-volume academic medical center.

METHODS Medical records from Brigham and Women's Hospital were retrospectively reviewed. Selected for study were 82 patients with CD who during April 2008–April 2014 had consecutively undergone transsphenoidal resection or who had subsequent pathological confirmation of ACTH-positive tumor staining. In addition to demographic, patient, tumor, and surgery characteristics, complications were evaluated. Complications of interest included syndrome of inappropriate antidiuretic hormone secretion, diabetes insipidus (DI), CSF leakage, carotid artery injury, epistaxis, meningitis, and vision changes.

RESULTS Of the 82 patients, 68 (82.9%) had CD and 14 (17.1%) had SCAs; 55 patients were female and 27 were male. Most common (n = 62 patients, 82.7%) were microadenomas, followed by macroadenomas (n = 13, 14.7%). A total of 31 (37.8%) patients underwent reoperation. Median follow-up time was 12.0 months (range 3–69 months). The most common diagnosis was ACTH-secreting (n = 68, 82.9%), followed by silent tumors/adenomas (n = 14, 17.1%). ACTH hyperplasia was found in 8 patients (9.8%). Of the 74 patients who had verified tumors, 12 (16.2%) had tumors with atypical features.

The overall (CD and SCA) rate of minor complications was 35.4%; the rate of major complications was 8.5% (n = 7). All permanent morbidity was associated with DI (n = 5, 6.1%). In 16 CD patients (23.5%), transient DI developed. Transient DI was more likely to develop in CD patients who had undergone a second operation (37.9%) than in those who had undergone a first operation only (12.8%, $p < 0.05$). Permanent DI developed in 4 CD patients (5.9%) and 1 SCA patient (7.1%). For 1 CD patient, intraoperative carotid artery injury required endovascular sacrifice of the injured artery, but the patient remained neurologically intact. For another CD patient, aseptic meningitis developed and was treated effectively with corticosteroids. One CD patient experienced major postoperative epistaxis requiring another operative procedure to achieve hemostasis. For 2 CD patients, development of sinus mucocoeles was managed conservatively. For 1 SCA patient, an abdominal wound dehiscence at the fat graft site. No patients experienced postoperative CSF leakage, visual impairment, or deep vein thrombosis.

CONCLUSIONS Transsphenoidal surgery is the treatment of choice for patients with CD and other ACTH-positive staining tumors. Recent advances in endoscopic technology and increasing surgeon comfort with this technology are making transsphenoidal procedures safer, faster, and more effective. Serious complications are uncommon and can be managed successfully.

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KEY WORDS endoscopic; endonasal; transsphenoidal; complications; Cushing's disease

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; DI = diabetes insipidus; GTR = gross-total resection; ICA = internal carotid artery; SCA = silent corticotroph adenoma; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

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CUSHING's disease (CD) is a hypercortisolemic state caused by the presence of a corticotroph-producing adenoma and accounts for 70%–80% of all cases of Cushing's syndrome in adults.³⁸ Less commonly, an adrenocorticotrophic hormone (ACTH)–secreting lesion located outside the hypophyseal system causes elevated serum cortisol levels. The most common locations for ACTH production in patients with Cushing's syndrome are the adrenal glands, lungs, liver, or ovaries.^{52,59} Cushing's syndrome can also arise iatrogenically, as a consequence of long-term glucocorticoid therapy.^{14,61}

Corticotroph-producing adenomas represent approximately 16% of all surgically resected pituitary tumors.²¹ Of patients with CD, women are more likely to harbor corticotroph-secreting adenomas; reported female-to-male ratios are 3–10:1.³⁴ Although corticotroph-secreting adenomas can occur in patients of any age, peak incidence is between the 3rd and 5th decades of life. Delays in CD diagnosis, management, and follow-up are common and lead to increased adverse metabolic complications and death. For optimal patient outcomes, rapid recognition, treatment, and vigilant monitoring are crucial.

If left unchecked, the combined clinical manifestations of CD increase a person's risk for increased illness and/or death while substantially reducing quality of life. The transsphenoidal approach for resection of corticotroph-secreting adenomas is associated with a high percentage of disease remission.^{46,55,63} After surgical treatment, some patients may experience persistent subclinical CD that remains difficult to detect with routine testing.²⁸ Complications (e.g., CSF leakage, deteriorated vision, epistaxis, headaches, and infection) are uncommon but potential adverse events after transsphenoidal operative procedures.^{41,45,50}

Silent corticotroph adenomas (SCAs) are defined by physiological cortisol secretion and ACTH-immunopositive staining without the autonomous ACTH secretion found in patients with CD.^{47,64} Unlike CD patients, SCA patients most commonly experience headache, visual field deficits, and subacute pituitary apoplexy.⁶⁴ Patients harboring SCAs do not experience supraphysiological levels of cortisol and therefore are not as prone to the numerous systemic ailments associated with CD.^{23,44} Some authors have reported that patients have increased aggression and that SCAs tend to recur and progress more than CD.^{20,33}

In this article, we describe the complications associated with the endonasal, transsphenoidal approach for the treatment of ACTH-positive staining tumors (CD and SCA) performed by 1 surgeon at Brigham and Women's Hospital, a high-volume academic medical center.

Methods

Of the 681 patients who had undergone transsphenoidal resection at Brigham and Women's Hospital from April 2008 through April 2014, medical records were reviewed for 82 who had either CD or SCA. We included patients with positive ACTH immunohistochemical staining results but without clinical diagnosis of CD. Endocrinologists at the Comprehensive Pituitary Center at the hospital verified the diagnosis of all patients with central

ACTH-dependent CD. All patients underwent endonasal transsphenoidal surgery performed by 1 surgeon (E.R.L.). Samples for laboratory testing were collected from all patients before surgery and on postoperative Days 1, 2, and 7; postoperative Months 3, 6, and 12; and every year thereafter. All patients underwent Gd-enhanced brain MRI for which there were high-resolution thin-cut pituitary sequences and reconstructions in 3 orthogonal planes. These MR images were obtained preoperatively, 3 months postoperatively, and annually thereafter.

Patient records were evaluated for basic demographic information (age, sex) and preoperative presentation (endocrine function, presenting symptoms, and any attempted medical therapy). Also evaluated were imaging characteristics (size, location, cystic nature, degree of invasion of local structures if body CT was used to screen for other sources of ACTH secretion), surgical characteristics (endoscopic vs microscopic procedure; use of fat graft, nasal packing, or lumbar drains), and surgical pathology findings (any atypia noted on histopathological examination, MIB-1 labeling index, immunohistochemistry results). Also recorded were laboratory results (serum cortisol, ACTH, other endocrine axes) and data on the patient's postoperative hospital course (length of stay, days spent in the intensive care unit, need for hormone replacement, postoperative endocrine function, extent of resection according to postoperative imaging, need for any adjuvant treatment).

Complications of interest were symptomatic syndrome of inappropriate antidiuretic hormone secretion (SIADH), diabetes insipidus (DI), epistaxis requiring reoperation or readmission, injury to the internal carotid artery (ICA), meningitis, CSF leakage, abdominal wound infection, new visual deficit, postoperative hemorrhage, mucocele formation, and 30-day postoperative readmission for any reason.

Basic patient demographics, preoperative characteristics, and perioperative characteristics were summarized by using counts and percentages for nominal variables and by using means/medians and standard deviations/ranges for continuous variables. Patients were categorized according to sex and further evaluated for substantial difference by sex in terms of tumor size (micro- vs macroadenoma), age, and highest preoperative cortisol level. Records were then examined for postoperative complications. Pathological characteristics (immunohistochemistry findings and MIB-1 indices) and postoperative complications were summarized by using counts and percentages or means and standard deviations as appropriate. Tests of significance were determined by using chi-square tests and Mantel-Haenszel odds ratios for nominal variables, Student t-tests for continuous variables, and ANOVA for continuous variables with more than 2 categories. The data were analyzed by using SPSS version 22 (IBM Inc.). For all analysis, an alpha level of less than 0.05 was considered statistically significant.

Results

Of the 82 patients with ACTH-positive staining tumors, 68 (82.9%) had CD and 14 (17.1%) had SCA; 55 were women (mean age 42.3, range 8–68 years) and 27 were men (mean age 46.5, range 10–70). Recurrent disease

developed after surgery for 29 patients: 26 at other institutions and 3 at ours. The mean preoperative serum cortisol level was 22.1 µg/dl (range 18.9–54.4 µg/dl) among patients with CD and 12.7 µg/dl (range 2.3–20.6 µg/dl) among patients with SCA. The median follow-up time was 12.0 months (range 3–69 months) (Table 1).

Cushing's Disease

Presentation

Among the 68 patients with CD, the most common presenting symptoms and signs were weight gain (n = 53, 77.9%), centripetal fat deposition (n = 42, 61.8%), fatigue (n = 36, 52.9%), hypertension (n = 31, 45.6%), skin changes (n = 29, 42.6%), and hair changes (n = 24, 35.3%). Acne was present in 7 patients (10.3%). Visual disturbance were the presenting symptoms in less than one-quarter of CD patients (n = 16, 23.5%). Among 48 female patients, galactorrhea was present in 4 (8.3%), fertility problems in 2 (4.1%), and dys- or amenorrhea in 19 (39.5%). Sexual dysfunction was reported by 8 CD patients (11.8%); less commonly reported were anxiety (n = 14, 20.6%), mood changes (n = 20, 29.4%), and cognitive dysfunction (n = 8, 11.8%). Cavernous sinus syndrome was uncommon (n = 2, 2.9%). One CD patient (1.5%) had signs of pituitary tumor apoplexy (Table 1).

Deficiencies in more than 2 other hormonal axes were found in 6 CD patients (8.8%). Most CD patients (n = 45, 66.1%) were receiving treatment for diabetes mellitus, 6 (8.8%) were taking thyroid replacement medication, 1 undergoing reoperation was taking growth hormone replacement medication, and another was taking desmopressin for DI (Table 1).

Imaging Characteristics

Of the 68 patients with CD, most (n = 60, 88.2%) had microadenomas, 2 (2.9%) had macroadenomas, and 6 (8.8%) had no adenomas visible on preoperative brain MR images. Only 2 patients (2.9%) had suprasellar extension, and 11 (16.1%) had tumors invading the parasellar and/or suprasellar structures (Table 2).

Perioperative Characteristics

Intraoperatively, an endoscope was used for 97.1% of CD patients and a microscope was used for 4.7% of CD patients (microscope was used exclusively for only 6 patients). Nasal packing was required in 28 patients (41.2%), and a lumbar drain was required in 1 patient (1.4%). An abdominal fat graft was used in 34 patients (50%) when a CSF leak was suspected or directly visualized at the time of resection. Gross-total resection (GTR) was achieved in 64 CD patients (94.1%). Postoperative admission to the intensive care unit was needed by 16 patients, and the average hospital stay was 3.3 ± 1.0 days (Table 3).

Silent Corticotroph Adenomas

Presentation

Among the 14 patients (17.1%) with SCA, the mean age was 51.6 years (range 27–70 years), which was older than that of CD patients (mean age 38.7 years). SCAs were present in 7 women and 7 men (50% each). Fewer SCA

patients (n = 2, 14.3%) than CD patients (n = 29, 42.6%) underwent surgery for recurrence (Table 1).

The most common presenting signs and symptoms among patients with SCA were headache (n = 10, 71.4%), visual impairment (n = 9, 64.3%), hypertension (n = 6, 42.9%), weight gain (n = 4, 28.6%), and pituitary apoplexy (n = 4, 28.6%). Sexual dysfunction was present in 3 patients (21.4%), cavernous sinus syndrome in 1 (7.1%), and evidence of osteoporosis in 2 (14.3%) (Table 1).

Preoperative thyroid replacement therapy was being received by 4 SCA patients (28.6%) and diabetes mellitus therapy by 8 (57.1%). The mean preoperative serum cortisol level among SCA patients was 12.7 µg/dl (range 2.3–20.6 µg/dl). The median follow-up time for patients with SCA was 24.0 months (range 3–69 months) (Table 1).

Imaging Characteristics

Most patients with SCA (n = 8, 57.1%) had macroadenomas. A tumor with radiographic evidence of tumor invasion was present in 1 patient (7.1%), cystic components in 1 (7.1%), and suprasellar extension in 2 (14.2%) (Table 2). For no patient with SCA were preoperative MR images of the brain interpreted as normal.

Perioperative Characteristics

All patients with SCA underwent an endoscopic transsphenoidal operation exclusively (n = 14, 100%). Abdominal fat grafting was performed in 8 patients (57.1%), nasal packing in 5 (35.7%), and placement of a lumbar drain in none. Gross-total resection was achieved in 11 SCA patients (78.6%). Postoperative admission to the intensive care unit was required by 1 (7.1%) SCA patient. Average hospital stay was 2.8 (SD = 1.1) days.

Postoperative Normalization of Serum Cortisol Levels in Patients With CD

Postoperatively, cortisol levels normalized on the first postoperative day for 72.4% of patients with recurrent CD tumors and 82.1% of patients with de novo CD. Cortisol levels normalized on the seventh postoperative day for more than 86% of patients with recurrent CD and 97.4% of those with de novo CD. These normalization rates were durable at 12 months (Table 4).

ACTH-Secreting Tumors

Surgical Pathology

Pathological examination of samples collected during surgery revealed CD and ACTH-positive staining tumors in 62 (75.6%) of the 82 patients. There were 14 patients (17.1%) with SCA. Atypical adenomas were found in 14 patients (17.1%): 7 (13.7%) of 51 patients with de novo and 7 (22.6%) of 31 patients with recurrent tumors. Patients with CD and SCA were also immunohistochemically positive for other hormones: 15 adenomas (18.3%) for prolactin, 13 (15.9%) for growth hormone, 6 (7.3%) for follicle-stimulating hormone, 8 (9.8%) for luteinizing hormone, and 5 (6.1%) for thyroid-stimulating hormone. The mean MIB-1 labeling index was 2.9% (range 1%–20%); no statistical difference was found between those undergoing their first or second operations. The MIB-1 labeling

TABLE 1. Preoperative characteristics of patients with CD and SCA

Characteristic	Patients w/ CD	Patients w/ SCA
No. of patients	68	14
Mean age, yrs (range)	38.7 (8–67)	51.6 (27–70)
Sex, no. (%)		
F	48 (70.6)	7 (50.0)
M	20 (29.4)	7 (50.0)
Recurrence, no. (%)	29 (42.6)	2 (14.3)
Cushing's syndrome symptoms, no. (%)		
Weight gain	53 (77.9)	4 (28.6)
Centripetal fat deposition	42 (61.8)	2 (14.3)
Muscle wasting	16 (23.5)	1 (7.1)
Skin changes*	29 (42.6)	0 (0.0)
Hair changes†	24 (35.3)	1 (7.1)
Hyperpigmentation	9 (13.2)	0 (0.0)
Acne	7 (10.3)	0 (0.0)
Hypertension	31 (45.6)	6 (42.9)
Osteoporosis	13 (19.1)	2 (14.3)
Growth retardation	9 (13.2)	0 (0.0)
Anxiety	14 (20.6)	1 (7.1)
Mood changes‡	20 (29.4)	1 (7.1)
Cognitive dysfunction§	8 (11.8)	0 (0.0)
Sexual dysfunction	8 (11.8)	3 (21.4)
Fertility problems	2 (2.9)	0 (0.0)
Dysmenorrhea/amenorrhea¶	19 (39.5)	2 (16.7)
General symptoms, no. (%)		
Headache	23 (33.8)	10 (71.4)
Visual disturbance	16 (23.5)	9 (64.3)
CN paresis		
Oculomotor (CN III)	2 (2.9)	1 (7.1)
Abducens (CN VI)	0 (0.0)	0 (0.0)
Pituitary tumor apoplexy	1 (1.5)	4 (28.6)
Hypopituitarism**	6 (8.8)	1 (7.1)
Galactorrhea	4 (5.9)	0 (0.0)
Fatigue	36 (52.9)	8 (57.1)
Incidental	0 (0.0)	1 (7.1)
Preop hormone replacement therapy, no. (%)		
Thyroid hormone	6 (8.8)	4 (28.6)
Testosterone	0 (1.5)	0 (0.0)
Growth hormone††	1 (1.5)	0 (0.0)
Desmopressin††	1 (1.5)	0 (0.0)
Diabetes medication	45 (67.3)	8 (59.3)
Adrenalectomy, no. (%)	1 (1.5)	0 (0.0)
Mean preop serum cortisol, µg/dl (range)	22.1 (18.9–54.4)	12.7 (2.3–20.6)
Median follow-up time, mos (range)	12.0 (3–48)	24.0 (3–69)

CN = cranial nerve.

* Bruising, abdominal striae, or thinning.

† Alopecia capitis or facial/truncal hirsutism.

‡ Depression, irritability, or impulsivity.

§ Memory problems or inattention.

¶ In 48 women.

** One or more derangements in other pituitary axes.

†† Replacement after surgery.

TABLE 2. Preoperative MRI characteristics of patients with CD and SCA

Tumor Characteristic	No. of Patients (%)	
	w/ CD	w/ SCA
Microadenoma	60 (88.2)	6 (42.9)
Macroadenoma	2 (2.9)	8 (57.1)
Invasive	7 (10.3)	1 (7.1)
Cystic	2 (2.9)	1 (7.1)
Parasellar	9 (13.2)	0 (0.0)
Suprasellar	2 (2.9)	2 (14.2)
No abnormalities	6 (8.8)	0 (0.0)

index is the fraction of tumor cells that are labeled by Ki 67 and is used as an index of proliferation. Hyperplasia was diagnosed in 8 patients (9.8%), and significantly more of these patients (7 [22.6%] of 31) underwent a second operation than underwent only a first operation (1 [2.0%] of 51; $p < 0.05$) (Table 5). Operative specimens were found to be normal gland in 6 patients (7.3%).

Complications

Minor Complications. The overall rate of minor complications (for CD and SCA patients) was 35.4%. Minor complications occurred in 24 CD patients (35.3%) and 5 SCA patients (35.7%). Transient symptomatic SIADH developed in 3 CD patients (4.4%) and no SCA patients. Transient DI developed in 16 CD patients (23.5%) and in a comparable percentage ($n = 3$, 21.4%) of SCA patients. However, transient DI was more likely to develop in CD patients after a second operation ($n = 11$, 37.9%) than after a first operation ($n = 5$, 12.8%, $p < 0.05$). Postoperative epistaxis developed in 1 CD patient, and sinus mucocoeles developed in 2. Transient postoperative visual blurring, which resolved spontaneously within 7 days, was reported by 1 patient; wound dehiscence occurred at the abdominal

TABLE 3. Perioperative characteristics of patients with CD and SCA

Characteristic	No. of Patients	
	w/ CD	w/ SCA
Technology used, no. (%)		
Microscope	10 (14.7)	0 (0.0)
Endoscope	66 (97.1)	14 (100.0)
Both	4 (7.6)	3 (12.5)
Intraop, no. (%)		
Fat graft/CSF leak	34 (50.0)	8 (57.1)
Nasal packing	28 (41.2)	5 (35.7)
Lumbar drain	1 (1.3)	0 (0.0)
Postop		
Mean op time, mins (SD)	195 (40.1)	201 (35.9)
ICU admission, no. (%)	16 (23.5)	1 (7.1)
Mean hospital stay, days (SD)	3.3 (1.0)	2.8 (1.1)
GTR, no. (%)	64 (94.1)	11 (78.6)

ICU = intensive care unit.

fat graft site in 1 patient; and self-limiting aseptic meningitis, which was treated symptomatically with steroids (Table 6), occurred in 1 patient.

Major Complications. The overall rate of major complications was 8.5% ($n = 7$). All permanent morbidity was associated with DI ($n = 5$, 6.1%). Permanent DI developed in 4 CD patients (5.9%) and 1 SCA patient (7.1%). For 1 CD patient, an intraoperative carotid artery injury required endovascular sacrifice of the injured artery, but the patient remained neurologically intact. For 1 CD patient, major postoperative epistaxis required another operative procedure to achieve hemostasis. For another CD patient, minor postoperative epistaxis was treated effectively with topical vasoconstrictors and nasal packing. No postoperative CSF leak, permanent visual loss, or deep vein thrombosis was reported for any patient (Table 6).

Discussion

Transsphenoidal surgery is a safe and effective treatment for patients with CD and SCA.^{5,13,16,41,45,49,50,53–55,58,61,63} Rates of GTR tend to be high in terms of diagnostic pathology^{16,42,51} and higher among patients with CD than with SCA.⁴⁷ This trend is probably associated with the diminutive size of CD adenomas compared with SCAs as well as the invasive nature of SCAs in general. In the series reported here, 88.2% of CD patients harbored microadenomas, and rates of GTR were 94.1%. In comparison, 57.1% of SCA patients had macroadenomas, and rates of GTR were lower (78.6%). Of note, only 1 patient had an invasive SCA, less than what has historically been reported in comparable series.⁴⁷ In a series of 23 patients with SCA, Scheithauer et al. found that all tumors were macroadenomas, 87% with suprasellar extension and 61% with radiographic evidence of cystic change.⁴⁷ In the series reported here, the tumor was discovered incidentally for 1 SCA patient, and tumors in 6 SCA patients were classified as microadenomas, which could account for the low incidence of invasion. For the remaining 7 SCA patients, 3 tumors (42.8%) were classified as cystic, suprasellar, or invasive.

Complications in patients undergoing a transsphenoidal operative procedure are rare but important to anticipate.^{41,50,55,66} The reported postoperative mortality rate is low, 0.4–2.0%,^{41,50,55,66} and none of the patients reported in our series died. Among patients undergoing transsphenoidal surgery for pituitary adenomas in general, the rate range of morbid complications is 3.3%–9.3%^{3,7,27} but tends to be higher among patients undergoing similar operative treatment for CD (range 9%–15%).^{1,7,11,36,41,50,54,55,58,63} In our series, the overall rate of minor complications (among CD and SCA patients) was 35.4%, and the rate of major complications was 8.5%. All permanent morbidity was associated with DI ($n = 5$, 6.1%); when patients with DI were excluded from analysis, the overall rate of major complications was 2.4% (Table 6).

In general, patients undergoing transsphenoidal surgery are at greater risk for complications if they harbor macroadenomas or if the surgery is a repeat operation for recurrent disease.^{1,7,30,36} We found that patients undergoing an operation for recurrent disease were 3.3 times more

TABLE 4. Postoperative normalization of serum cortisol levels in 68 patients with CD

Perioperative Day	Serum ACTH Cortisol (pg/ml)*	Serum Cortisol Level (μg/dl)	Normal Cortisol Level, no. (%)†
1st TSS, 39 patients			
Mean preop (range)	169 (11–3351)	23.4 (18.1–75.6)	13 (33.3)
POD1‡		12.5 (0.8–54.4)	32 (82.1)
POD2‡		11.4 (0.8–29.6)	35 (89.7)
POD7‡		10.9 (1.0–27.9)	38 (97.4)
12 mos postop	69 (5–88)	9.0 (0.8–36.8)	37 (94.9)
2nd TSS, 29 patients			
Mean preop (range)	118 (10–887)	20.3 (17.1–36.0)	9 (31.3)
POD1‡		15.4 (0.6–40.4)	21 (72.4)
POD2‡		11.9 (0.6–28.5)	26 (89.7)
POD7‡		12.8 (0.8–39.5)	25 (86.2)
12 mos postop	114 (5–982)	11.3 (0.1–81.1)	25 (86.2)

POD = postoperative day; TSS = transsphenoidal surgery.

* Reference range 10–60 pg/ml.

† Reference range 2.3–19.4 μg/dl.

‡ Sixty-six patients were followed up for at least 12 months (mean 16.5 months, range 12–69 months).

likely to experience a complication than were those undergoing surgery for de novo disease (OR 3.3, $p = 0.015$) (Table 6). However, this association was driven by transient DI, and when these patients were removed from the analysis, there was no longer a significant difference between the 2 groups. There does, however, seem to be an association between repeat surgery and development of transient DI in CD patients (OR 3.1, $p = 0.04$) (Table 6).

Use of endoscopic transsphenoidal pituitary surgery is slowly but steadily replacing use of microscopic approaches. The overall rates of complications with microscopic^{8,16,18,50,56} and endoscopic approaches^{14,44,67,73,77,79} for treatment of CD seem to be similar. The best study for comparing the microscopic approach to the current endoscopic approach was published in 1999 by the senior author (E.R.L.).⁵⁰ Among 105 patients with CD in that

study (the historical series), the mortality rate was 0.9%, and the permanent morbidity rate was 1.8%. The overall rate of complications in that series of patients was 13.3%, compared with 35% in the series reported here. Most of the CD complications among patients who underwent the endoscopic approach were associated with transient natriuretic imbalance (79% of minor complications). Incidence of permanent DI was higher among patients in our series (5.8%) than among those who underwent the microscopic approach for CD (1.0%). It is possible that greater visualization through endoscopy has led to greater manipulation of the pituitary gland and thus higher rates of postoperative dysnatremia. The endoscopic approach used in this series resulted in no nasal septal perforations compared with 2 perforations among patients in the historical series who underwent the microscopic approach. Incidence of

TABLE 5. Pathology of tissue surgically collected from patients with CD or SCA who underwent transsphenoidal surgery

Characteristic	No. of Patients (%)		
	1st TSS (n = 51)	2nd TSS (n = 31)	All (n = 82)
Immunohistochemistry			
ACTH (CD)	35 (68.6)	27 (87.1)	62 (75.6)
Silent ACTH	12 (23.5)	2 (6.5)	14 (17.1)
Follicle-stimulating hormone	2 (3.9)	4 (12.9)	6 (7.3)
Luteinizing hormone	4 (7.8)	4 (12.9)	8 (9.8)
Human growth hormone	8 (15.7)	5 (16.1)	13 (15.9)
Prolactin	10 (20.0)	5 (16.1)	15 (18.5)
Thyroid-stimulating hormone	2 (3.9)	3 (9.7)	5 (6.1)
Atypical	7 (13.7)	7 (22.6)	14 (17.1)
Hyperplasia	1 (2.0)	7 (22.6)	8 (9.8)*
Normal gland	4 (7.8)	2 (6.4)	6 (7.3)
Mean proliferation index (MIB), % (range)†	3.1 (1.0–20.0)	2.6 (1.0–15.6)	2.9 (1.0–20.0)

* $p < 0.05$.

† The MIB-1 labeling index is the fraction of tumor cells that are labeled by Ki 67 and is used as an index of proliferation.

TABLE 6. Postoperative complications in patients with CD (categorized by first or second operation) and SCA*

Complication	Patients w/ CD		All CD Patients (n = 68)	Patients w/ SCA (n = 14)
	1st TSS (n = 39)	2nd TSS (n = 29)		
Minor				
Transient symptomatic SIADH	1 (2.6)	2 (6.9)	3 (4.4)	0 (0.0)
Transient DI	5 (12.8)	11 (37.9)	16 (23.5)†	3 (21.4)
Epistaxis	0 (0.0)	1 (3.4)	1 (1.3)	0 (0.0)
Sinus-related (mucocoele)	1 (2.6)	1 (3.4)	2 (2.7)	0 (0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Transient visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Abdominal wound dehiscence	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Aseptic meningitis	1 (2.6)	0 (0.0)	1 (1.3)	0 (0.0)
30-day readmission	1 (2.2)	0 (0.0)	1 (1.3)	0 (0.0)
Total			24 (35.3)	5 (35.7)
Major				
Permanent DI	1 (2.6)	3 (10.3)	4 (5.9)	1 (7.1)
Postop CSF leak	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bacterial meningitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Reoperation (epistaxis)	0 (0.0)	1 (3.4)	1 (1.5)	0 (0.0)
Carotid artery injury	1 (2.6)	0 (0.0)	1 (1.5)	0 (0.0)
Permanent visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total			6 (8.8)	1 (7.1)

* Values are presented as the number (%) of patients.

† $p < 0.05$.

deep vein thrombosis was higher among patients undergoing microscopic transsphenoidal surgery in the historical series ($n = 4$, 3.8%) than among those undergoing the endoscopic approach in our series ($n = 0$). As a result of his experience with deep vein thrombosis, and after publishing the former study in 1999, the senior author began giving aspirin (81 mg) to patients 1 day after transsphenoidal surgery. The absence of deep vein thrombosis among patients in the current series probably reflects this change in treatment strategy.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Symptomatic hyponatremia is a reported complication of transsphenoidal surgery (2.1%–9.0%).^{17,19,25,40,60} CD patients in particular seem to be at the same risk for postoperative development of symptomatic hyponatremia. Semple and Laws reported a 5.7% incidence of postoperative hyponatremia in CD patients.⁵⁰ We report a 4.4% ($n = 3$) rate of transient symptomatic SIADH in CD patients. Symptomatic, delayed hyponatremia associated with SIADH is poorly understood but is thought to be associated with postoperative release of stored antidiuretic hormone from traumatized nerve terminals within the pituitary gland.^{17,25,39,40,60} Other factors that can drive postoperative hyponatremia include cerebral salt wasting, excessive fluid intake, and low dietary sodium intake.³⁹

Diabetes Insipidus

One of the most common forms of transient perturbation of fluid homeostasis after transsphenoidal procedures

is central DI. The reported overall incidence of postoperative transient DI is 8.7%–18.3%; persistent DI requiring long-term treatment with desmopressin develops in 2.0%–12.4% of patients.^{26,36,48} Patient and operative factors that have been associated with the development of permanent DI include intraoperative CSF leakage and resection of a craniopharyngioma and/or Rathke's cleft cyst.^{12,26,32,35,48} Transient postoperative DI has been associated with repeated operation for recurrent disease, CD, and microadenoma.^{36,48}

Among the patients in our series, transient postoperative DI requiring treatment with desmopressin during hospitalization developed in 16 CD patients (23.5%). Undergoing a second surgery for recurrence was found to be a significant predictor of development of this condition in CD patients ($n = 11$, 37.9%) compared with CD patients undergoing their first operation ($n = 5$, 12.8%, $p < 0.05$). Permanent DI developed in 4 CD patients (5.9%), among whom all had microadenomas, 2 had an intraoperative CSF leak, and 3 were undergoing their second operation. Transient postoperative DI developed in 3 (21.4%) SCA patients; permanent DI later developed in 1 of these patients.

Apart from the potential neurological sequelae of untreated DI, many patients are at risk for readmission to the hospital for stabilization and treatment of hypernatremia. In the series reported here, the only person readmitted was a CD patient with DI.

Carotid Artery Injury

One of the major complications associated with the en-

donasal endoscopic transsphenoidal procedure is injury to the ICA, which can be one of the most devastating complications for the patient.¹⁵ Injuries to the ICA have been associated with both microscopic and endoscopic endonasal approaches, and incidence of injury ranges from 0.4% to 3.8%.^{1,57} The consequences of ICA injury can range from being innocuous to fatal. Potential vascular sequelae of ICA violation include formation of pseudoaneurysms, carotid cavernous fistulas, postoperative vasospasm, and even vascular occlusion resulting in clinical ischemia and stroke. A recent meta-analysis highlighted vascular injury as an uncommon but important complication of transsphenoidal approaches.^{1,29}

In the series reported here, only 1 CD patient experienced intraoperative injury to the cavernous carotid artery. The hemorrhage was tamponaded, and the patient was immediately transferred to the endovascular suite for a diagnostic angiogram and subsequent sacrifice of the affected artery. The patient recovered well from the complication, without any neurological deficit. As of the 3-year follow-up examination, no untoward, delayed intracranial complication had developed.

Infections

Infections after transsphenoidal surgery are rare. The 3 most common forms of postoperative infection are meningitis, sinusitis, and dehiscence of the abdominal fat graft wound. Bacterial meningitis occurs in 0.4%–1.8% of transsphenoidal surgery patients.^{2,3,7,24,43} CD patients are known to be prone to infection before surgery, but rates of postoperative meningitis among these patients seem to be similar to rates among patients with other pituitary tumors.⁴³ No bacterial meningitis developed in any patient in our series, but aseptic meningitis developed in 1 patient. Symptoms resolved after oral administration of corticosteroids.

In patients who undergo an abdominal fat graft, the abdominal wound can be at risk for dehiscence, hematoma formation, and infection. This occurrence is rare, however, even in large series.²¹ In 1 SCA patient in our series, an abdominal wound dehiscence, and the patient was given a short course of oral antibiotics, with successful resolution.

Vision Changes

Visual loss after transsphenoidal surgery can result from direct neural injury, devascularization, or compression. More specifically, proximal, postoperative causes of visual impairment are thought to be direct injury to (or devascularization of) any portion of the optic apparatus, an occult fracture of the bony orbit that causes compression of neural elements, a postoperative hematoma compressing the optic chiasm, cerebral vasospasm causing hemodynamic ischemia, and/or prolapse of the optic chiasm into an empty sella.

The range of visual loss after transsphenoidal surgery reported for most series is 0.2%–1.2%.¹ In our series, a transient, subjective decrease in visual acuity was experienced by 1 patient; neuroophthalmological evaluation on postoperative Day 2 revealed normal efferent and afferent function. The patient's visual blurriness was attributed to blood pressure fluctuations and endocrine derangement and resolved without treatment 1 week after surgery.

Epistaxis

Epistaxis after transsphenoidal surgery can be severe and can have a substantial detrimental effect on patient outcomes. Epistaxis can be either immediate or delayed; delayed epistaxis occurs an average of 10 days after surgery.^{2,3,9} Immediate postoperative epistaxis has been associated with ICA injury and acute postoperative hypertension; delayed epistaxis has been associated with anterior ethmoidal artery injury and postoperative anticoagulation.⁹ Treatment for epistaxis depends on its severity and can range from bedside nasal packing to endovascular embolization and/or reoperative exploration.⁹

In our series, minor epistaxis in 1 CD patient was successfully treated with bedside nasal packing. Spontaneous epistaxis occurred in another CD patient while exercising 5 weeks after the operative procedure. The patient sought care at the emergency room and was taken to the operating room for endoscopic exploration. A small hemorrhagic source from the inferior margin of the septectomy was subsequently cauterized and overlain with Surgicel (Ethicon Incorporated, Johnson & Johnson). The patient was discharged without further issue. Neither patient suffered any long-term adverse sequelae of epistaxis.

Sinus Mucocoele

Sinus-related complications after transsphenoidal surgery are uncommon; incidence is 1.2%–6.2%.^{4,31} Sinusitis and/or sinus mucocoeles can form postoperatively and are thought to be associated with infection, necrosis of fat graft, remnant bone fragments, and mechanical/thermal trauma to the mucosa.³¹ Lu et al.³¹ correlated the size of the bony window opened in the face of the sphenoid sinus with postoperative sinus complications. They reported higher incidence of sinus-related complications among patients with small sphenoidotomies, decreased frequency of routine postoperative nasal care, and postoperative foreign debris accumulation in the sphenoid sinus. For avoiding these complications, they recommended removal of at least two-thirds of the sphenoid face, regular nasal hygiene, and meticulous removal of bony fragments.³¹ For patients with rhinosinusitis/mucocoele that is refractory to medical management, the next management step is early surgical drainage. If these complications are left untreated or undertreated, they can progress into fulminant bacterial meningitis.

In our series, nasal mucocoeles, without overt sinusitis, developed in 2 CD patients. For both patients, the mucocoeles resolved with regular nasal hygiene with saline spray and without any further procedures.

CSF Leak

A CSF leak occurs as a postoperative complication in 0.6%–10% of transsphenoidal surgery patients.^{2,3,22,57} Reported predictors of postoperative CSF leakage include large tumors, invasion of sella diaphragm, craniopharyngioma and Rathke's cleft cyst pathologies, tumor adherence, presence of arachnoid diverticulum, suprasellar tumor extension, and extended skull-base approaches.^{19,22,57} Chee et al. reported CSF leakage rates of 7.4% among patients with CD exclusively.⁶

With the proper identification and intraoperative attention, the rate of postoperative CSF leakage can be drastically reduced. Among patients in our series, no postoperative CSF leaks occurred. However, weeping intraoperative CSF leaks were suspected in 42 patients (51.2%), and therefore for each patient, the sella was packed with an abdominal fat graft. A lumbar drain was placed in 1 patient with a recurrent, invasive tumor after induction of anesthesia and before surgery. An intrathecal drain was used for the injection of air to encourage intraoperative tumor subsidence and for postoperative CSF diversion to treat an anticipated, generous leak. After tumor resection, a sellaplasty with an epidural synthetic plate was fashioned to the specifications of the sellar opening. A sellaplasty can also be fashioned from the nasal septum. Gelfoam (Pfizer) pledgets were then laid over the synthetic plate so that it was not in direct contact with sphenoid sinus air.

Deep Venous Thrombosis

Although patients undergoing transsphenoidal operations are at low risk for the development of deep vein thrombosis (2.5%), the risk for those with CD is reportedly higher (range 5.5%–5.9%).⁵⁰ Overall, the risk for development of venous thromboembolism is more than 10-fold higher for patients with hypercortisolemia than for their age-matched counterparts without hypercortisolemia.⁶² The hypercoagulable state in hypercortisolemic patients is thought to be associated with increased procoagulant production, coagulation cascade activation, and impaired fibrinolytic capacity. The result of these cascade perturbations is a shortened activated partial thromboplastin time and a subsequently increased time required for thrombolysis.⁶²

Of note, deep vein thrombosis was not diagnosed for any patients in our series. Before induction of anesthesia, all patients were fitted with bilateral, lower extremity sequential compression devices, which they wore for the remainder of their hospital stay. In conjunction with these devices, CD patients also received aspirin (81 mg) starting on postoperative Day 1 and continuing for 6 weeks. All patients were encouraged to dorsiflex/plantarflex their feet while in bed and were mobilized the day after surgery. No patient received heparin products for chemoprophylaxis against formation of deep vein thrombosis. This algorithm has essentially eliminated symptomatic postoperative deep vein thrombosis in CD patients.

This study has a number of limitations. First, it was a retrospective chart review and, as such, is subject to all biases attendant to this study design. Second, the definition of CD remission is variable, and the data reported here represent serum cortisol normalization, which could artificially inflate remission rates in the short term because patients with residual disease could have serum cortisol levels in the “normal” range. Third, this patient population may not be representative of the other CD and SCA populations. Many of these patients are referred for consultation because of diagnostic ambiguity, anatomical complexity, or residual/recurrent disease; therefore, their treatment results may not reflect the outcomes of other patients.

Conclusions

Transsphenoidal surgery is the treatment of choice for patients with CD or SCA. Recent advances in endoscopic technology and increasing surgeon comfort with this technology are making transsphenoidal procedures safer, faster, and more effective. Permanent morbidity is rare, and serious complications, although uncommon, can be managed successfully.

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