Neurosurgical Treatment of Cushing Disease

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KEYWORDS

• Cushing syndrome • Cushing disease • Transsphenoidal surgery • Adrenocorticotropin • Hypercortisolism

KEY POINTS

- Cushing syndrome (CS) refers to the clinical and metabolic effects of excess systemic glucocorticoids; Cushing disease (CD), or adrenocorticotropin (ACTH) overproduction by an adrenal adenoma or carcinoma, is the most common cause of endogenous CS.
- CD is largely a surgical disease, with microscopic and endoscopic transsphenoidal surgery enjoying similar success rates and relatively low complication rates.
- Remission rates following surgery are 70% to 95%, although the literature demonstrates significant variability in the definition of remission.
- Recurrence following surgery occurs 2% to 20% of the time, after 2 to 10 years.
- Recurrences may be treated with reoperation, radiosurgery, or radiation therapy; interim medical therapy is required in the latter 2 cases.

INTRODUCTION

Cushing syndrome (CS) refers to the constellation of physiologic effects of excess systemic glucocorticoids, including impaired glucose tolerance, skin and bone fragility, compromised immunity, and cardiovascular complications, to name a few. Untreated CS is associated with mortality rates greater than 5 times that of matched controls,[1–4] whereas proper treatment normalizes mortality risk.[5]

Whereas the most common cause of CS is the administration of exogenous steroids, endogenous CS is a consequence of adrenocorticotropin (ACTH) overproduction by a pituitary adenoma or an ectopic tumor, or cortisol overproduction by autonomous adrenal abnormalities. Overproduction of ACTH by a pituitary adenoma (or, rarely, carcinoma) is the most common of these, and is known as Cushing disease (CD).

DIAGNOSIS

Patients who should be considered for evaluation of possible CS/CD include those with unusual features for their age (including early-onset hypertension, low bone mineral density for age, fractures after minimal trauma, oligomenorrhea in premenopausal-aged women, to name a few), those who manifest multiple features suggestive of cortisol excess over time (including central adiposity, hyperglycemia, spontaneous ecchymoses, wide or darkly pigmented striae, proximal muscle weakness, edema, hypokalemia, thromboembolic events, psychiatric manifestations, and recurrent, opportunistic, or atypical

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infections), children with delay in linear growth, and patients with incidentally found adrenal or pituitary masses.

Once the diagnosis of CS/CD is considered, laboratory testing is aimed at establishing (or refuting) the presence of pathologic hypercortisolism (Fig. 1). After the diagnosis of CS is established on a biochemical basis, a thorough, systematic approach is required to identify the underlying cause (pathologic lesion) with the goal of curative resection, if possible.[6,7]

Establishing the Diagnosis of Cushing Syndrome

Laboratory testing is needed to confirm the presence of CS, and distinguish it from other conditions (Box 1).[8,9] The physiologic principles underlying laboratory testing for CS include excessive cortisol secretion leading to increased cortisol excretion in the urine (24-hour urine free cortisol [UFC]), blunting of the normal circadian rhythm of cortisol secretion leading to high nocturnal (nadir) cortisol levels (measured in the blood or saliva), and decreased sensitivity of the hypothalamic-pituitary-adrenal axis to negative feedback exerted by glucocorticoids, leading to lack of suppression of early-morning serum cortisol after the oral administration of dexamethasone (dexamethasone suppression testing).[8,9]

Measurement of UFC is optimally performed using liquid chromatography followed by tandem mass spectrometry or high-performance liquid chromatography, and provides a reliable estimate of endogenous cortisol secretion in patients with normal kidney function.[8,10] Several (at least 2–3) specimens should be collected to achieve adequate (95%) sensitivity.[8,10] Measuring urine creatinine excretion in the specimen is recommended to ensure adequacy of collection. In addition, urine volume should be recorded and high fluid intake (>5 L daily) discouraged during collection, as high urine volume is associated with high UFC.[11] A 4-fold or greater UFC above the upper end of the normal range is

Box 1
Conditions associated with clinical and/or biochemical evidence of hypercortisolism

- Cushing syndrome (endogenous or exogenous)
- Pregnancy
- Psychiatric conditions (including major depression)
- Severe obesity
- Poorly controlled diabetes mellitus
- Alcohol dependence
- Familial glucocorticoid resistance
- Physical illness, including trauma or surgery[a]
- Strenuous regular exercise[a]
- Anorexia nervosa[a]
- Excessive serum cortisol binding globulin levels (including women taking oral contraceptives)[a]

[a] Clinical features of Cushing syndrome are generally absent.

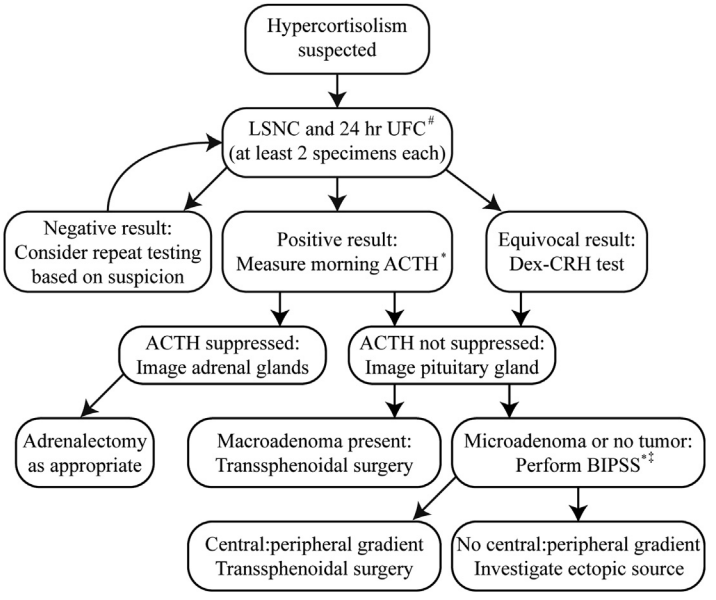

Fig. 1. An approach to the diagnosis of suspected Cushing syndrome and Cushing disease. A flow chart depicting a suggested diagnostic algorithm for determining the etiology of hypercortisolism is presented. # The 1-mg dexamethasone suppression test may also be considered (see text for details). * Testing to be conducted during periods of biochemical hypercortisolism. † Patients whose plasma ACTH levels are not fully suppressed may undergo a (peripheral) CRH stimulation test to fully establish if Cushing syndrome is ACTH dependent. ‡ The 8-mg dexamethasone suppression test and the (peripheral) CRH stimulation test may be helpful in some patients (see text for details). *Abbreviations:* ACTH, adrenocorticotropin; BIPSS, bilateral inferior petrosal sinus sampling; Dex-CRH test, dexamethasone-suppressed corticotropin-releasing hormone stimulation test; LNSC, late-night salivary cortisol; UFC, urine free cortisol.

pathognomonic of CS.[10] However, cortisol excess of lesser magnitude may also occur in other conditions, which need to be distinguished from CS (see **Box 1**).[8,10] Using the upper end of the UFC reference range as the diagnostic cutpoint, the specificity of this test for CS is 81%.[10]

Measurement of late-night (11 PM) salivary cortisol (LNSC) is accurate in the diagnosis of CS.[8,12,13] Collection of at least 2 salivary specimens is advised for adequate test sensitivity (92%–100%).[8,12,13] The specificity of LNSC for CS is 93% to 100% in outpatient populations.[8,12,13] However, there are limited validating data in hospitalized patients.[14] Individuals with altered circadian activities, including third-shift workers, may have falsely elevated LNSC.[8,12,13] Midnight serum cortisol can be measured in sleeping or awake patients, but is cumbersome and has not been validated in the acutely ill.[8]

Dexamethasone suppression tests (DST) in common use include the overnight, 1-mg DST and the 2-day, 2 mg/d DST.[7,8,10] Using a cutpoint of 1.8 μg/dL for early morning (8–9 AM) serum cortisol, the overnight, 1-mg DST has sensitivity exceeding 95% with specificity of 80%. Falsely elevated results may occur in patients with any of the conditions in **Box 1**, or among individuals taking medications that can accelerate dexamethasone clearance.[8] Measuring serum dexamethasone is advised to ensure sufficient exposure to dexamethasone. Using serum cortisol end points, the 2-day, 2-mg/d DST has comparable sensitivity with the overnight, 1-mg DST, but is cumbersome and requires adequate patient instruction.[7,8,10]

The dexamethasone-suppressed, corticotropin-releasing hormone (CRH) stimulation test may help distinguish between CS and other conditions (pseudo–Cushing states) associated with cortisol excess (see **Box 1**). This test is cumbersome, but can be helpful in patients whose prior laboratory investigations for hypercortisolism have yielded inconsistent results, or patients suspected of having other conditions associated with hypercortisolism (including major depression). Initial reports suggested that this test has 100% sensitivity and specificity in the diagnosis of CS, using a cortisol cutpoint of 1.4 μg/dL at 15 minutes after CRH administration.[15] However, more recent findings suggested that the diagnostic performance of this test is less than perfect, especially in patients taking medications that increase dexamethasone clearance.[16]

Distinguishing Between Causes of Cushing Syndrome

Once CS is confirmed, additional testing is needed to identify the underlying cause (**Box 2**).[7,9,10,12]

Box 2
Etiology of Cushing syndrome

ACTH-Dependent Cushing Syndrome

Pituitary tumor (adenoma, or rarely carcinoma); Cushing disease (70%)

Ectopic ACTH secretion (10%)

Ectopic CRH secretion (rare)

ACTH-Independent Cushing Syndrome

Adrenal adenoma (10%)

Adrenal carcinoma (5%)

Macronodular adrenal hyperplasia (1%–2%)

Primary pigmented nodular adrenal disease (1%–2%)

McCune-Albright syndrome (1%–2%)

Measuring plasma ACTH in early-morning specimens distinguishes between ACTH-dependent and ACTH-independent causes in most patients, as plasma ACTH levels usually exceed 20 pg/mL in the former group and are usually less than 5 pg/mL in the latter.[9,10] Patients with intermediate ACTH levels may undergo a (peripheral) CRH stimulation test to fully establish if CS is ACTH dependent.

Patients with ACTH-dependent CS most often have an underlying pituitary corticotroph adenoma or, very rarely, carcinoma (CD), but may sometimes have an ectopic tumor secreting either ACTH or, rarely, CRH (see **Box 2**).[7,10,17]

Pituitary corticotroph tumors are microadenomas in the vast majority (90%) of patients with CD. High-resolution magnetic resonance imaging (MRI) using a pituitary protocol detects a sellar mass in 60% to 70% of CD patients.[10,12,18] However, it should be noted that incidental sellar hypodensities of small size (<10 mm) are present in approximately 10% of individuals in the general population.[19] Therefore, the presence of a presumed microadenoma does not assure that it is the source of ACTH excess.

Two dynamic tests proposed to distinguish between pituitary and ectopic sources of ACTH excess include the high-dose (8-mg) DST and the (peripheral) CRH stimulation test, and can be helpful in some patients.[7] The 8-mg DST has 81% to 82% sensitivity and 67% to 79% specificity for CD.[9,10] The CRH stimulation test has 70% to 93% sensitivity and 88% specificity for CD.[9,10,20] As the pretest probability of CD exceeds 85% among patients with ACTH-dependent CS, neither test has adequate diagnostic accuracy, when performed alone.[9] Of note, patients with concordant positive results on 8-mg DST and the (peripheral) CRH

stimulation test have an approximately 98% probability of having a corticotroph tumor, but likely represent a minority (35%) among patients with ACTH-dependent CS.[10,21]

Bilateral inferior petrosal sinus sampling (BIPSS) with measurement of plasma ACTH levels before and after CRH administration has a 94% sensitivity and specificity, using a cutpoint (peak central/peripheral ACTH ratio) of 2:1 before CRH or 3:1 after CRH administration.[10,22,23] This test is considered the gold standard for distinguishing between pituitary and ectopic sources.[10,22,23] However, the test requires considerable expertise to be performed reliably and safely, and has been rarely associated with thrombotic or neurologic complications.[10] As anomalous venous drainage or incorrect sampling may mitigate the diagnostic performance of this test, it is imperative that both the venous anatomy and accurate catheter positioning in the inferior petrosal sinuses be verified before and after specimen collection to ensure appropriate sampling. Measuring serum prolactin level in specimens may also help improve the diagnostic accuracy of this test.[24–26]

Patients with ACTH-dependent CS who are suspected of having an ectopic source should undergo imaging studies, including computed tomography (CT) and MRI examinations of the neck, chest, abdomen, and pelvis, whole-body scintigraphy using indium-111–labeled pentetreotide, or positron emission tomography in combination with CT. Tumors associated with ectopic ACTH-dependent CS lesions are frequently small (**Box 3**), and may not be detected despite extensive imaging examinations in up to 19% of patients.[17]

Additional laboratory tests may be helpful in localizing an occult ectopic tumor, including tests for serum CRH, calcitonin, chromogranin A, fractionated plasma metanephrines, and 24-hour urine 5-hydroxyindoleacetic acid.[17] A recommended approach to the diagnosis of CS/CD is outlined in **Fig. 1**.

Box 3
Tumors most frequently associated with ectopic ACTH syndrome

- Foregut carcinoid (bronchopulmonary, thymic)
- Small cell lung carcinoma
- Pancreatic or appendiceal carcinoid
- Medullary thyroid carcinoma
- Islet cell tumor
- Undifferentiated neuroendocrine tumor
- Pheochromocytoma
- Olfactory esthesioneuroblastoma

SURGICAL OPTIONS

CD is a surgical disease, with reported remission rates ranging from the high 60s to high 90s[18,27–33] following transsphenoidal surgery. Surgical options include microscopic approaches via either sublabial[34] or endonasal[35] exposure, as well as the endoscopic approach.[36] While some centers continue to use the sublabial approach,[37] the endonasal is the more common of the microscopic approaches because of the decreased incisional morbidity. Recurrences may be treated with repeat transsphenoidal surgery, as well as radiosurgery or radiation therapy with interim medical therapy until radiation therapy takes effect.[38] Refractory cases may be considered for bilateral adrenalectomy.

Microscopic Endonasal Approach

The microscopic approach offers the advantage of a binocular stereoscopic view with superior optics. After induction of general anesthesia, the patient is positioned supine with the head on a gel headrest or in 3-point fixation. Navigation is provided by either fluoroscopy or frameless stereotaxy.

The posterior septal mucosa is infiltrated with local anesthetic containing epinephrine, and incised opposite the middle turbinate. The mucosa is lifted with a periosteal elevator, and the posterior septum fractured. A piece of the bony septum may be retained for later use. A self-retaining nasal speculum provides retraction as the anterior wall of the sphenoid sinus is drilled to provide enough room for later insertion and manipulation of appropriately sized curettes.

The sella is identified, paying attention to remain midline, using the location of bony septations and the carotid impressions in the superolateral walls of the sphenoid sinus as guides. A laser Doppler probe may be used to help identify the position of the cavernous carotid arteries, especially in cases of medially located cavernous sinuses.[39–41] The central region of entry into the sella is chosen, and the shell of bone over the face of the sella is thinned with a drill and removed with microcurettes and Kerrison punches. The dura is bipolarly coagulated and sharply opened in a cruciate fashion.

Tumor fragments are dissected free and delivered from the sella using an assortment of ring curettes. Because approximately 90% of tumors in CD are microadenomas,[42] care should be taken to obtain sufficient specimen for histopathological analysis. The surface of the pituitary gland is closely inspected for residual fragments of adenoma. If no

obvious tumor is visualized, serial frozen-section biopsies are performed. If these remain negative, some advocate for hemi-hypophysectomy on the side predicted by the preoperative BIPSS.[43]

Following resection, hemostasis is obtained with oxidized cellulose or other hemostatic agents. Fat harvested from a separate abdominal incision is used to pack the sella, which is then covered with a piece of previously harvested septal bone, titanium mesh, or other synthetic plug. If cerebrospinal fluid (CSF) leak is suspected, a layer of fibrin glue or other sealant may be applied. The mucosal flap is reapproximated, and the nasal passage inspected before completion of the procedure.

Endoscopic Approach

The endoscopic approach offers the advantage of a wider field of view and the capacity to inspect regions of the sella with angled fiber bundles. Access into the sphenoid sinus is similar to that described above, although a nasal speculum is not required. The majority of situations favor a 0° degree 4-mm endoscope, which can be affixed to the operating table with an articulating arm or held by the assistant, allowing the surgeon to use conventional bimanual techniques.

Recent improvements in endoscope technology have provided much clearer high-definition visualization compared with the early monocular endoscopes. Three-dimensional videoscopes are also being developed. Several centers have reported remission rates similar to those of microscopic approaches.[36,44–50]

OUTCOMES

Initial Remission

One challenge in identifying success rates of transsphenoidal surgery for CD is that no standardized remission criteria exist. Varying stringencies of criteria used may contribute to observed variations in remission rates (**Table 1**). Proposed biochemical criteria for remission include low or undetectable serum cortisol, low plasma ACTH, low 24-hour UFC, low or normal cortisol following dexamethasone suppression, and combinations of these variables.[5,28,29,51–53]

Timing of postoperative laboratory investigation also varies, with some studies defining remission by hormone levels as much as 6 months postoperatively, whereas others characterize remission by values obtained early after the operation. In general, remission rates of 67% to 97% are reported.[5,28,29,42,52–66] Although pediatric CD is rare, similar remission rates have been documented in pediatric populations.[60,67,68]

A strategy of early repeat operation in patients with initial treatment failure has been investigated and shown to result in remission in 67% to 71% of patients with treatment failure after initial operation.[69,70] In such cases, positive BIPSS may be important to confirm the presence of pituitary adenoma. Because CD has serious associated morbidity and mortality and postponing a repeat operation may increase technical difficulty owing to scar tissue and altered anatomy,[71] early reoperation may offer substantial benefits. Conversely, complications such as hypopituitarism and CSF leak may be higher with repeat operation,[69,70] and occasional patients may achieve delayed remission in the weeks after the initial procedure, suggesting that reexploration should not be considered until the postoperative cortisol levels have plateaued in a persistently elevated range.[33]

Factors Predicting Initial Remission

Several factors have been linked to likelihood of successful outcome. A body of evidence points to higher remission rates in surgical patients with microadenomas than in those with macroadenomas,[5,42,53,59,62,72] although other studies have failed to find such a difference.[55,58] Overall, larger tumors may have worse outcomes,[28,60,73] even within the macroadenoma category alone,[74] perhaps because larger adenomas are more likely to be invasive. Patients with invasive tumors are less likely to achieve remission after transsphenoidal surgery.[61,75] Invasion of the cavernous sinus or suprasellar tumor extension results consistently in a higher incidence of persistent disease.[28,74]

Intraoperative identification of an adenoma is an important positive prognostic factor,[42,57,76,77] and allows selective adenomectomy to be performed rather than a potentially more morbid procedure such as partial or total hypophysectomy. Intraoperative ultrasonography has been successfully used to increase intraoperative adenoma localization and results in higher remission rates in some reports.[78] Identification of adenoma on preoperative MRI,[58] histopathology,[42,54,55,57,63] both MRI and intraoperatively,[53] or MRI and histology together[57] have also been linked to improved chance of remission. Failure to identify an adenoma may signal unusual pathology or misdiagnosis of a condition such as pseudo-CS that is unlikely to be cured by pituitary surgery, but in the presence of strict diagnostic criteria is more likely related to an incomplete exploration, or an undetected and invasive tumor.

Initial transsphenoidal surgery is often reported to have a higher chance of success than repeat surgery performed for treatment failure or

Table 1
Published surgical series for CD with remission and recurrence rates

Authors,[Ref.] Year	N	Follow-Up (mo)	Remission Rate (%)	Definition of Remission[a]	Recurrence Rate (%)	Time to Recurrence (mo)
Ciric et al,[94] 2012	136	69.9	83.4	Cortisol <5.3 Steroid requirement	9.4	80.3
Honegger et al,[59] 2012	83	38.2	84.3	Normal or decreased UFC Cortisol <2 with LDDST	6.7	37
Sun et al,[95] 2012	119	36.8	86.6	Cortisol ≤5 60mo cortisol ≤normal Normal UFC Suppression with LDDST	4.9	38.9
Yamada et al,[96] 2012	124	60	90.3	Cortisol ≤5 or Cortisol ≤2 with LDDST	3.6	45
Lindsay et al,[84] 2011	331	126	98.2	Cortisol <5	12	50.4
Ammini et al,[55] 2011	97	18–132	66.7	Cortisol <5	18.5	25.2
Storr et al,[68] 2011	183	N/S	72.2	Cortisol ≤normal	22.9	N/S
Alwani et al,[97] 2011	45	56.5	67	Suppression with LDDST Normal UFC Steroid requirement	6.7	13.5
Valassi et al,[33] 2010	620	45	76.1	UFC <80 Cortisol normal Cortisol <5 with LDDST	13	N/S
Jagannathan et al,[66] 2009	261	84	97	UFC or cortisol ≤normal	2.3	56
Fomekong et al,[58] 2009	40	86	80	Normal UFC Steroid requirement	9.4	54
Patil et al,[82] 2008	215	45	85.6%	Normal UFC Steroid requirement	17.4	39
Prevedello et al,[77] 2008	167	39	80	Cortisol and UFC ≤normal	13	50
Atkinson et al,[98] 2008	42	30	86	Hypocortisolism	11.1	57.6
Hofmann et al,[42] 2008	426	72.3	68.5	Cortisol ≤2 LDDST	15	73.2
Rollin et al,[62] 2007	108	72	83.3	Steroid dependence Cortisol <3 with LDDST Clinical remission	6.8	44
Acebes et al,[54] 2007	44	49	89	Clinical remission Cortisol and UFC ≤normal	7.7	54.6
Esposito et al,[53] 2006	40	33	80	Cortisol ≤5	3.1	21

Atkinson et al,[56] 2005	63	115.2	71.4	UFC ≤127 Cortisol suppressed after LDDST	22.2	62.4
Salenave et al,[99] 2004	54	19.9	82.7	Cortisol ≤3.5 11-desoxycortisol <10 μg/dL in metyrapone test Negative insulin tolerance test Peak cortisol <20 after CRH stimulation Normal UFC Cortisol <2.7 with LDDST	19.5	19.9
Hammer et al,[28] 2004	289	133.2	82	Cortisol ≤5 basally or with LDDST UFC ≤normal	9	58.8
Pereira et al,[80] 2003	78	86	72	Steroid dependence or clinical remission Cortisol <3.6 with LDDST 2 consecutive normal UFC	9	84
Flitsch et al,[100] 2003	147	61	93	Cortisol ≤normal	5.5	44
Chen et al,[72] 2003	174	>60	80	Cortisol ≤3	6.3	27
Yap et al,[65] 2002	97	92	68.5	Cortisol undetectable (<2)	11.5	36.3
Shimon et al,[63] 2002	82	50.4	78	Clinical remission UFC normal Cortisol <5 with LDDST	5	44
Rees et al,[61] 2002	53	72	77	Cortisol <2	5	24.5
Chee et al,[57] 2001	61	88	78.7	Cortisol normal Clinical remission Cortisol <3.6 with LDDST	14.6	76.1
Barbetta et al,[52] 2001	68	57.5	90	Cortisol and UFC ≤normal Normal LDDST Steroid requirement	21	36
Swearingen et al,[5] 1999	161	96	85	Cortisol <5 UFC <20	7	68.4
Semple and Laws,[87] 1999	105	N/S	75.2	Cortisol <normal Steroid requirement	N/S	N/S
Invitti et al,[29] 1999	236	28	69	Cortisol and UFC ≤normal	17	115

Abbreviations: LDDST, low-dose dexamethasone suppression test; N/S, not specified.
[a] Units for cortisol are μg/dL, units for UFC are μg/24 h.

recurrence.[5,29,42,53,62] Repeat surgery may also be associated with a higher rate of complications such as CSF leak.[53] However, some studies specifically addressing the issue of repeat surgery have found a substantial remission rate of 62% to 87.5%,[63,76,79] thus surgical intervention should not be excluded in patients with treatment failure or recurrence.

Several biochemical parameters have been proposed to predict remission. Early postoperative cortisol[75] and ACTH levels may have prognostic value. In one study, ACTH greater than 34 pg/mL on postoperative day 1 had sensitivity of 80% and specificity of 97.4% for not achieving remission within 6 months, whereas cortisol greater than 20 μg/dL had sensitivity of 100% and specificity of 90%.[54] Another study found that patients who had less than 3 μg/dL cortisol on postoperative day 3 following low-dose dexamethasone suppression retained 93% remission at 5 years, whereas those who merely normalized cortisol had all experienced recurrence by that time.[72] Pereira and colleagues[80] suggested that a cortisol level below 5 μg/dL measured at 3 months after surgery is the optimal cutoff for predicting remission at 6 months with sensitivity of 94% and specificity of 79%. Preoperative ACTH has been reported to be higher in patients with postoperative hypercortisolemia.[74]

Several technical factors may contribute to operative success. One group reported using the pseudocapsule formed by compressed normal anterior pituitary cells as a surgical capsule in encapsulated adenomas confined to the anterior pituitary. This technique gave excellent results, with initial remission of 96.6% and 100% following early repeat surgery for initial treatment failures,[66] with a recurrence of only 2.3% at a mean of 7 years. A technique using preoperative MRI and BIPSS for localization and intraoperative frozen sections achieved 100% remission in 18 patients.[81] The contribution of surgical experience to surgical success is somewhat controversial, with several studies showing no changes in outcome over a surgeon's career,[42,57] and several others reporting improvement with experience.[61,65]

Recurrence

Despite initial surgical success, several patients develop recurrent disease. Because patients can develop recurrent disease many years after initial surgery, the rate of recurrence depends on the length of follow-up. Recurrent disease appears in 3% to 22% of patients at a mean of 1.75 to 9.6 years.[5,28,29,52–58,61–63,65,77,80]

As in the case for initial remission, the criteria for determining recurrence are also variable.

Recurrence continues to increase over time with long-term follow-up.[28,29,56,77,80,82] For example, one study showed recurrence of 0.5%, 6.7%, 20.8%, and 25.5% at 1, 2, 3, and 5 years, respectively, and ultimate recurrence of 46% in patients followed for at least 5 to 13 years. Recurrence may be higher in repeat operations. A study of early repeat surgery for failed initial transsphenoidal adenoma resection reported a 30% recurrence rate, perhaps reflecting a more treatment refractory characteristic of this subset of patients.[70] The recurrence rate may also be spuriously elevated if initial remission criteria were too lax, such as inclusion of patients with normal cortisol, because such patients may never have actually achieved initial remission.

Factors Predicting Recurrence

The vast majority of recurrent tumors are located at the same or adjacent location to the original tumor, suggesting that microscopic tumor remnants are the cause of many recurrences.[76,83] Histologic evidence of dural invasion has been reported in 45.4% of surgeries for pituitary adenomas; therefore, undetected dural invasion may contribute to unnoticed and unresected tumor tissue.[73,83] Dural invasion increases with adenoma size, patient age, and male gender.[73] Microadenomas may recur at a lower rate than macroadenomas,[5] perhaps because they are less likely to be invasive. However, conflicting evidence exists on this point, with one small study showing excellent long-term remission rates in patients with macroadenomas,[51] and several studies showing no difference in recurrence rates between microadenomas and macroadenomas.[65]

Postoperative cortisol and ACTH levels have been studied as predictors of long-term remission. Some investigators have found that patients with hypocortisolism in the postoperative period have lower rates of recurrence than subjects with normalized cortisol,[52,74,82] and that patients with long-term remission have lower cortisol levels on postoperative days 3 to 5.[84] One study found 97% sustained remission in patients with serum cortisol less than 5 μg/dL within the first 2 postoperative days, albeit with a relatively brief follow-up of 33 months.[54] Another study reported no recurrence during a median follow-up period of 40 months in patients who had undetectable postoperative serum cortisol.[85] However, undetectable postoperative cortisol does not exclude the chance of recurrence at a later date,[56,65] and in one study where postoperative cortisol predicted remission at 6 months, it was not related to long-term remission.[80] Some studies have suggested

subnormal ACTH as a predictor of sustained remission, whereas others have not found this measure to be particularly useful.[53] High postoperative ACTH as well as cortisol and ACTH levels following CRH stimulation have been related to recurrence.[29,84]

COMPLICATIONS

Overall, transsphenoidal surgery for CD has a rate of serious morbidity of 1.8% to 15% and mortality of 0% to 1.9%.[5,28,61,62,65,80,86,87] A nationwide study of inpatient data found in-hospital mortality of 0.7%, 2.9% adverse outcomes (death or discharge other than to home), and morbidity of 42.1% following transsphenoidal surgery for CD.[88] However, untreated CD also results in significant morbidity and mortality, making appropriate treatment essential. Patients who are successfully surgically treated have long-term mortality similar to the general population,[5] whereas those with persistent disease have increased mortality.[28] Patients with CD who undergo transsphenoidal surgery may have higher immediate and delayed complication rates than patients with other pituitary tumors who undergo this operation,[89] perhaps because of the higher incidence of medical comorbidities in the CD population and the effects of cortisol withdrawal.

Endocrine

Hypothalamic-pituitary-adrenal axis dysfunction (adrenal insufficiency) is anticipated after successful transsphenoidal surgery for CD, and is generally reversible within 6 to 18 months postoperatively. Deficiency of at least one pituitary hormone is reported in 8.6% to 53% of patients.[5,28,61,62] Hypopituitarism likely depends on the procedure performed, with much lower rates in selective adenomectomy and increasing rates with extensive exploration.[59] In some series the rate approaches 100% for subtotal or total hypophysectomy.[79] The rate of hypopituitarism may also be increased in repeat surgeries.[62]

Normal corticotroph function is inhibited by adenoma hypersecretion and thus patients will require glucocorticoid replacement following successful surgery, although normal cortisol function is usually regained within 6 to 18 months.[90] The timing of initiation of glucocorticoid replacement varies between centers. Some physicians prefer to observe patients for biochemical or clinical hypocortisolism before initiating glucocorticoid replacement therapy, whereas others begin patients on a low-dose glucocorticoid immediately following surgery, allowing earlier discharge with outpatient follow-up to determine pituitary function and remission status.[51]

Diabetes insipidus (DI) is one of the most common postoperative endocrine disturbances. Transient DI occurs in 6% to 75% while permanent DI is less common and generally occurs in 1% to 15%, requiring long-term use of desmopressin.[5,28,29,53,56–59,61–65,75,77,86,87] Secretion from the syndrome of inappropriate antidiuretic hormone also occurs fairly frequently, so patients should be monitored for hyponatremia. Deficiency of new gonadotropin, thyroid, and growth hormone can also occur.

Neurologic

Neurologic symptoms occur in 5.6% of patients.[88] Vision loss may occur because of damage to the optic apparatus or its vasculature as well as vasospasm,[91] and occurs in 0.7% to 4% of patients.[58,61,86,87] Cranial nerve injury most commonly occurs from exploration of the cavernous sinus, with damage most frequently occurring to the sixth cranial nerve.[87] A 0.7% rate of cranial nerve injury has been reported nationally.[88] Cranial nerve palsies may be transient or permanent. A risk of carotid artery injury exists and has been reported at 0% to 2.5%.[53,75,86]

Infectious

Chronic sinusitis may occur in as many as 1.5% to 8.5% of patients.[66,86] Antibiotics are the first line of treatment, but up to half of patients may require surgical intervention to achieve cure.[92] Meningitis is a serious complication that is uncommonly observed postoperatively but is an associated risk of CSF leak. Incidence is reported at 0.4% to 7.9%.[28,56,64–66,86] Patients who have packing of the surgical cavity with a fat graft have a risk for infection or wound breakdown at the graft donor site.

CSF Rhinorrhea

CSF rhinorrhea may be apparent intraoperatively or postoperatively. It is treated by CSF drainage with a lumbar drain, and packing with a fat graft if noted intraoperatively or in persistent cases. If conservative measures fail, reexploaration is required. This complication occurs in 0% to 13% of patients.[5,28,56,57,61,63,64,66,77,86–88]

Nasal Complications

Patients may develop postoperative epistaxis. Occasionally the bleeding is severe enough to require nasal packing or vessel cauterization. Severe epistaxis occurs in 0.4% to 3.4% of patients.[5,53,57,66,86,87] Perforation of the nasal

septum can occur with certain surgical approaches. Incidence has been reported at 1.6% to 9.3%.[57,75,86,87]

Thromboembolic

Thromboembolic disease may occur at a higher rate in CD than in other surgical patients, because of a hypercoagulable state that occurs with hypercortisolism as well as the greater rate of obesity associated with CD. Thus it is important that patients undergoing transsphenoidal surgery for CD receive appropriate deep vein thrombosis (DVT) prophylaxis, such as sequential compression devices and/or subcutaneous low molecular weight heparin. DVT or pulmonary embolism has been reported in 1% to 6% of cases.[56,58,61,65,75,87,93] Before treatment, patients with CD have an incidence of thromboembolic disease of 14.1 per 1000 person years.[93] CD patients have a higher postoperative rate of thromboembolic events than patients undergoing pituitary surgery for nonfunctioning adenomas.[93]

SUMMARY

Given the significant morbidity of untreated CS, it is imperative to determine its cause and begin therapy in a timely fashion. CD, or overproduction of ACTH by a pituitary adenoma, remains for the most part a surgical disease, with high remission rates and low complication rates following either microscopic or endoscopic transsphenoidal surgery. Reoperation, radiosurgery, and radiation therapy with interim medical therapy are options for recurrences, with bilateral adrenalectomy reserved for failures of other treatments. New medical treatments may hold promise as well (see the article by Fleseriu elsewhere in this issue on Medical management of persistent and recurrent CD).

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