Cushing's disease: pathobiology, diagnosis, and management

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Cushing's disease (CD) is the result of excess secretion of adrenocorticotrophic hormone (ACTH) by a benign monoclonal pituitary adenoma. The excessive secretion of ACTH stimulates secretion of cortisol by the adrenal glands, resulting in supraphysiological levels of circulating cortisol. The pathophysiological levels of cortisol are associated with hypertension, diabetes, obesity, and early death. Successful resection of the CD-associated ACTH-secreting pituitary adenoma is the treatment of choice and results in immediate biochemical remission with preservation of pituitary function. Accurate and early identification of CD is critical for effective surgical management and optimal prognosis. The authors review the current pathophysiological principles, diagnostic methods, and management of CD.

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CUSHING's syndrome (CS) is caused by prolonged supraphysiological levels of circulating cortisol. Cushing's disease (CD) is the most common etiology (70%–80% of CS cases) of endogenous CS. It is caused by a pituitary adenoma that secretes adrenocorticotrophic hormone (ACTH), which stimulates secretion of cortisol by the adrenal glands. If not effectively treated, CD is associated with hypertension, diabetes, obesity, osteoporosis, vascular disease, and shortened life span. Successful resection of a CD-associated ACTH-secreting pituitary adenoma results in immediate biochemical remission and preservation of pituitary function. Early identification of CD by clinical findings, endocrinological evaluation, and imaging studies is critical for diagnosis and effective surgical management.

Endocrinological and Clinical Features

Endocrinological Features

Normal Physiology

Insight into the normal and pathophysiological mechanisms of control of the hypothalamic–anterior pituitary–adrenal axis is critical to understanding the pathologic, di-

agnostic, and therapeutic features of CD (Fig. 1).⁵² Under normal physiological conditions (circadian rhythm, where cortisol levels peak in early morning and nadir late at night), systemic inflammation (cytokine), or stress (physiological or psychological), corticotropin-releasing hormone (CRH; a 41–amino acid peptide) is released from the paraventricular hypothalamic nucleus via the median eminence. From the median eminence, CRH is transported in the hypophyseal portal venous system to the pituitary gland, where it binds to the CRH receptor-1 (CRH-R1) on pituitary corticotroph cells. CRH binding to CRH-R1 receptors activates adenylate cyclase and stimulates proopiomelanocortin (*POMC*) gene expression in the corticotroph cells.^{17,66} Proopiomelanocortin preprohormone is processed into ACTH (a 39–amino acid peptide) and β -lipotropin (a 93–amino acid peptide). Products of β -lipotropin include β -endorphin and α -lipotropin. ACTH is secreted into the systemic circulation and binds to receptors in the adrenal cortex, where it stimulates production and secretion of glucocorticoids, including cortisol.⁸³ Under normal conditions, circulating cortisol provides physiological control of this endocrine axis by its negative feedback inhibition on hypothalamic CRH and pituitary ACTH secretion.¹⁰⁶

ABBREVIATIONS ACTH = adrenocorticotrophic hormone; CD = Cushing's disease; CRH = corticotropin-releasing hormone; CRH-R1 = CRH receptor-1; CS = Cushing's syndrome; IPSS = inferior petrosal sinus sampling; SPGR = spoiled gradient recalled; SRS = stereotactic radiosurgery.

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FIG. 1. Hypothalamic-pituitary-adrenal axis in healthy individuals and CD patients. **Left:** Under normal physiological circumstances, including circadian rhythm (diurnal secretion that peaks in early morning and nadirs near midnight) and stress (physiological and psychological), the paraventricular nucleus of the hypothalamus releases CRH (orange arrows), which the hypophyseal portal venous system transports to the anterior pituitary gland. In the pituitary gland, CRH stimulates pituitary corticotroph cells (orange arrow) by binding to CRH-R1 receptors to stimulate production and excretion of ACTH into the systemic circulation. ACTH then stimulates the adrenal cortex (red arrow) to synthesize and excrete glucocorticoids, including cortisol. Cortisol inhibits this endocrine axis (blue arrows) at the hypothalamus and pituitary by binding to glucocorticoid receptors and reducing CRH and ACTH production/secretion, respectively. **Right:** Under the pathophysiological conditions associated with CD, a benign monoclonal basophilic adenoma of the anterior pituitary gland continuously (resulting in loss of normal diurnal secretory rhythm) secretes excess levels of ACTH (large red arrow). Circulating ACTH drives supraphysiological production and secretion of cortisol from the adrenal cortices (large blue arrows) that results in reduced CRH production/excretion by the hypothalamus. While the ACTH-secreting adenomas in CD retain CRH-R1 and vasopressin receptors with their associated stimulatory capacity (adenomas secrete ACTH [large red arrow] when stimulated by CRH or desmopressin [large blue arrows]), the cortisol-driven negative feedback on the pituitary is significantly blunted. Nevertheless, very high levels of exogenous steroid (e.g., high-dose dexamethasone test response) suppress ACTH production by CD adenomas (small red arrow) and downstream circulating cortisol levels (small blue arrows). Copyright OSU Health Sciences Library Medical Visuals. Published with permission.

CD Pathophysiology

CD is caused by a benign monoclonal pituitary corticotroph adenoma that secretes excessive ACTH,³⁹ which causes supraphysiological secretion of glucocorticoids from the adrenal glands. The excess circulating cortisol disrupts the normal physiological diurnal variation in cortisol levels and exerts negative feedback inhibition on CRH secretion from the hypothalamus. However, the adenoma itself is relatively resistant to inhibition by endogenous circulating cortisol (Fig. 1). Consequently, CD is associated with suppressed secretion of CRH and elevated levels of ACTH in relation to the degree of cortisol production.

Clinical Features

Epidemiology

CD has a prevalence of 39.1 per million inhabitants (incidence 1.2–2.4 newly diagnosed cases per 1 million persons per year).^{31,55} The average age at diagnosis for adults is in the 4th decade (younger in females [mean 30.5 years] than males [mean 37.1 years]). The average age at diagnosis in pediatric CD is approximately 13 years (symptom onset 10.6 years).^{50,58,60} Symptom initiation to diagnosis averages 2–3 years in pediatric and adult cases.^{58,113} Before puberty, the ratio of female-to-male cases is similar (1:1).^{50,58} In adult CD patients, females are more frequently affected than males (3:1 vs 5:1).^{70,82,105,113}

Clinical Findings

Prolonged excessive cortisol exposure leads to multi-system signs and symptoms. The most common clinical features in adults include obesity, diabetes, hypertension, moon facies, and facial plethora (Fig. 2).^{70,82} While the most common findings in prepubertal pediatric patients include rapid weight gain, obesity, and decreased linear growth, the most common findings in postpubertal pediatric patients are rapid weight gain, dorsal/subclavicular fat pads, and amenorrhea.^{50,58,60,100} Psychiatric deficits (depression, emotional lability, anxiety, psychosis, panic attacks, suicidal ideation, and paranoia) and neurocognitive deficits (learning impairment and memory deficits) can also be associated with CD and may be the only sign/symptom in a subset of patients.^{51,69}

CD-Associated Morbidity and Mortality

CD-associated morbidity includes cardiac and cerebrovascular events, immunosuppression, osteoporosis, psychiatric disturbances, and diabetes. Untreated CD has an estimated standardized mortality ratio (ratio of observed CD-related deaths to expected deaths in the general population) of 1.9–4.8.^{21,31,40,55,111} CD-associated morbid risk factors are substantially reduced with successful treatment,^{21,42,102} but effectively treated patients may have a higher frequency of diabetes, obesity, and dyslipidemia

FIG. 2. Clinical features of CD. The hypercortisolism associated with CD leads to potent clinical signs and symptoms. Common signs and symptoms in adults include weight gain, obesity, diabetes, facial plethora, moon facies, menstrual irregularities, and hirsutism. Common prepubertal signs and symptoms in pediatric patients include rapid weight gain, obesity, and decreased linear growth. The most common postpubertal signs and symptoms in pediatric patients include rapid weight gain, dorsal/subclavicular fat pad, and amenorrhea. Copyright OSU Health Sciences Library Medical Visuals. Published with permission.

compared with controls. While many studies indicate that CD-associated mortality is returned to general population rates after biochemical remission,^{21,42,102} other studies have shown an elevated cardiovascular risk of death up to 5 years after successful biochemical remission. Psychiatric and neurocognitive disturbances can persist in some patients after successful treatment.^{4,23,37,69,87} Patients with persistent CD after treatment suffer increased morbidity and mortality.^{42,103}

Diagnosis

Biochemical Diagnosis

Diagnosis of CS

After exogenous sources are ruled out, clinical suspi-

cion of CS leads to laboratory assessment to confirm the presence of endogenous hypercortisolism (Fig. 3). Established guidelines for the diagnosis of CS recommend verification of hypercortisolism by 2 screening tests. Screening tests include late night salivary cortisol, 24-hour urine free cortisol, or low-dose dexamethasone suppression (1 mg overnight or 2 mg over 48 hours) testing.⁷²

Establishing the Cause of Hypercortisolism

After the diagnosis of CS is established, its cause is sought. Endogenous hypercortisolism can be caused by either an ACTH-dependent (pituitary adenoma or ectopic tumor) or independent (adrenal tumor) mechanism (Fig. 3).^{6,70} Plasma ACTH levels are obtained to assess for ACTH dependency as the cause of hypercortisolism. Inappropriately elevated ACTH levels in a hypercortisolemic state (i.e., greater than 10 pg/ml) are consistent with an ACTH-dependent cause (Fig. 3).

After the isolation, sequencing, and synthesis of CRH by Vale and colleagues in 1983,¹⁰⁶ CRH stimulation was introduced as a diagnostic test for the differential diagnosis of ACTH-dependent causes of CS (Fig. 1).^{19,43,70,73,78} This strategy was based on the assumption that CD is caused by well-differentiated adenomas derived from pituitary corticotrophs and that these adenomas should have receptors for CRH and the cellular constituents necessary to respond to CRH stimulation (a positive response is set arbitrarily at a 50% or more increase in ACTH and 20% or more increase in cortisol). Alternatively, ectopic ACTH-secreting tumors are derived from nonpituitary tissues and generally do not respond to CRH. However, there is an approximately 10% incidence of false-negative and false-positive results in ectopic tumors with CRH stimulation testing.^{43,73}

High-dose dexamethasone suppression testing also can be used to distinguish between ACTH-dependent causes of CS.^{19,43,54,70,73} Similar to the biological basis for CRH stimulation testing, dexamethasone suppression testing takes advantage of the presence of cellular constituents necessary to respond to dexamethasone (suppression) in the pituitary adenoma corticotroph cells and the lack of the negative feedback response in ectopic nonpituitary tumors that secrete ACTH (Fig. 1). In this manner, high doses (8 mg) of dexamethasone can suppress cortisol (i.e., a 50% or more decrease) secretion in approximately 80% of CD patients but the majority of ectopic ACTH-secreting tumors typically do not respond. However, a significant overlap in responses of pituitary and ectopic tumors to high-dose dexamethasone suppression testing compromise the diagnostic accuracy of this test.^{34,43,73}

MR Imaging

Because of their potent biological/clinical effects, CD-associated pituitary adenomas are often discovered when they are small. Data from large surgical series indicate that over 90% of ACTH-adenomas are microadenomas (< 1 cm in diameter) with a mean diameter of 6 mm at time of diagnosis.^{46,58} However, the small adenoma size and a reduced signal-to-noise imaging ratio at the sella-sphenoid bone-air interface contribute to the 40%–60% lack of detection of CD-associated adenomas on MR imaging at time of clinical and biochemical diagnosis.^{20,46} To best

FIG. 3. Diagnostic assessment of hypercortisolism. CS diagnostic testing: Guidelines for assessment of cortisol production in patients with clinical features of hypercortisolism (CS) advocate measurement of late-night salivary cortisol, 24-hour urine free cortisol, or low-dose dexamethasone suppression testing (1 mg overnight or 2 mg over 48 hours). Elevated levels of cortisol by these screening tests are consistent with CS. CS differential diagnostic testing: ACTH levels distinguish between ACTH-independent and ACTH-dependent causes of CS. Suppressed levels of ACTH are consistent with ACTH-independent causes (approximately 15%–20% of CS patients). ACTH-independent etiologies include adrenal adenomas, adrenal carcinomas, or adrenal hyperplasia, and are delineated by CT or MR imaging of the adrenal glands. Normal or elevated levels of ACTH are consistent with ACTH-dependent causes of CS (70%–80% of cases). Cortisol suppression after high-dose dexamethasone, cortisol, and ACTH responses to CRH stimulation and MR imaging revealing a pituitary adenoma (40%–60% of CD cases) are consistent with CD, and patients are referred for pituitary surgery. ACTH-dependent patients who do not suppress with high-dose dexamethasone suppression testing or stimulate cortisol production with CRH stimulation testing may have an ectopic ACTH-secreting tumor (10%–15% of cases). Ectopic ACTH-secreting tumors, including pulmonary and other carcinoid tumors, can usually be detected and localized by body imaging. ACTH-dependent patients with discordant results of the noninvasive differential diagnostic tests and/or with negative pituitary MR imaging undergo inferior petrosal sinus sampling to determine if hypercortisolism is from a pituitary adenoma (CD).

detect CD-associated adenomas on MR imaging, spoiled gradient recalled (SPGR) acquisition MR sequences are used. High-resolution (1- to 1.5-mm slice thickness) SPGR

MR imaging enhances detection of ACTH-secreting pituitary adenomas by 15%–30% compared with other available MR imaging sequences (Fig. 4).^{7,18,81}

FIG. 4. Coronal postcontrast MR images of the pituitary gland in a 6-year-old boy with CD. Preoperatively, standard T1-weighted (**left**) and SPGR MR (**right**) images were performed. While T1-weighted MR imaging did not reveal an adenoma, SPGR MR imaging clearly demonstrates a 3-mm adenoma (right, *arrowheads*). At surgery, an adenoma was found precisely in the location revealed by SPGR MR imaging. Complete resection was achieved, resulting in biochemical remission.

Inferior Petrosal Sinus Sampling

Diagnostic Evaluation

The pituitary gland drains laterally into the cavernous sinuses and then into the inferior petrosal sinuses. ACTH has a short half-life that results in an ACTH concentration gradient between the inferior petrosal veins and the peripheral blood. Consequently, more concentrated blood can be sampled from the direct venous drainage of the pituitary (via the inferior petrosal veins) compared with sampling from the systemic venous system. To better enhance central to peripheral differences in pituitary secretory substances (including ACTH), CRH stimulation was introduced during inferior petrosal sinus sampling (IPSS). Combining IPSS with CRH stimulation reduced the incidence of false-negative findings compared with systemic sampling.⁷³

Since the cavernous sinus blood often remains on one side as it enters the petrosal venous system, sampling from only one petrosal sinus has limited diagnostic utility.^{28,34,75} A combination of facts (i.e., the increased sensitivity of detecting ACTH secretion from a corticotroph adenoma, the stimulation response of the adenoma to CRH, and the potential for the venous blood to remain on one side of the inferior petrosal sinus in many patients) leads to the introduction of CRH stimulation with bilateral simultaneous IPSS for the differential diagnosis of CS. Furthermore, because of the frequent ipsilateral lateralization of pituitary gland drainage, lateralization of ACTH concentration in the inferior petrosal sinuses identified by bilateral assessment can also assist in the lateralization of adenoma within the pituitary gland in some cases (see *IPSS Lateralization for Localization of ACTH Adenomas in CD* below).^{34,75}

While false-negative and false-positive results are associated with IPSS, most diagnostic errors with IPSS are false-negative results in CD patients who do not have a central-to-peripheral concentration gradient (ratio of central-to-peripheral ACTH levels) of basal ACTH that is 2.0 or more, or 3.0 or more after CRH stimulation.^{33,45,80,93,110} This is often a result of unsuccessful placement of the intravascular catheter tips in the inferior petrosal sinuses. To avoid this problem, proper placement of intravascular catheter tips can be routinely confirmed by retrograde venography of the cavernous sinuses and inferior petrosal sinuses. The consistency of success with bilateral sampling of the inferior petrosal sinuses is operator dependent and varies substantially from center to center, from nearly uni-

versal success at some centers^{33,38,110} (including pediatric patients) to success rates of 67%–84% at others.^{49,96}

Most CD patients with a false-negative result can be identified by their relatively low peak ACTH levels in the inferior petrosal sinus blood (less than 200 pg/ml basal levels or less than 400 pg/ml after CRH stimulation).^{75,110} The relative concentration of prolactin in the inferior petrosal sinus blood compared with the peripheral blood can be used to normalize the concentration of the ACTH from the inferior petrosal sinuses in relation to the peripheral blood to yield a calculated ACTH in the inferior petrosal sinus-to-peripheral blood ratio that can enhance the diagnostic accuracy of the test.^{33,65,93} For this reason, many centers save blood samples from the procedure and measure the prolactin concentrations if the results of the IPSS need further analysis. To avoid false-positive results, IPSS must be performed while the patient is hypercortisolemic. If IPSS is performed in the absence of sustained hypercortisolism, the normal corticotrophs are not suppressed and will respond to CRH. The resulting inferior petrosal sinus-to-peripheral ACTH gradient will suggest CD, regardless of the etiology of CS and in normal subjects.^{80,112} Thus, during the eucortisolemic phase of cyclic CS or while under medical therapy to block cortisol production, false-positive results occur.

The initial results of IPSS for the differential diagnosis of CS suggested that the diagnostic accuracy of IPSS was 100%.^{34,75} However, later experience from many centers has indicated that, although the test is the most accurate endocrine test for the differential diagnosis of ACTH-dependent CS, it is now generally accepted to have a diagnostic accuracy in the range of about 95% at most institutions with a large CS experience.^{33,49,80,93} Although the largest experience with bilateral IPSS is with CRH stimulation, corticotroph tumors also respond to desmopressin, which can be used for the test if CRH is unavailable (Fig. 3).^{16,59}

IPSS Lateralization for Localization of ACTH Adenomas in CD

In the first small series, it appeared that bilateral IPSS (indicated by a side-to-side basal ratio of 1.4 or more) would permit prediction of the side of the pituitary gland that contained an ACTH-secreting microadenoma.^{61,72} However, later experience has shown that the lateralization accuracy of the test is in the range of 70%^{75,110} and the highest predictive value for lateralization is associated with consistent lateralization before and after CRH stimulation.¹¹⁰

Complications of IPSS

Venous infarction of the brainstem with permanent, serious neurological deficits can occur during IPSS.^{38,64} Thus, most centers of expertise in the evaluation and treatment of CS use IPSS only in patients with ACTH-dependent CD and conflicting results of noninvasive endocrine evaluation for the differential diagnosis of CS, discordant biochemical and radiological studies, or negative pituitary MR imaging (Fig. 3).⁸⁰

Cyclical CS and CD

Since the report by Liddle and colleagues in 1973,¹² it

has been apparent that the exceptionally rare patient with clinical features of CS may have cycles of excess glucocorticoid production that occurs every few days, weeks, or months. During cycles of normal cortisol production, endocrine testing to establish the diagnosis of CS or the differential diagnosis of it can be misleading. Consequently, it is important to recognize the potential diagnostic dilemma associated with such patients, especially since cyclical CS may accompany CD, ectopic ACTH-producing tumors, or cortisol-secreting adrenal tumors. The diagnostic strategy in cyclical CS is clinical follow-up with repeated testing, relying on testing midnight salivary cortisol and 24-hour

urine free cortisol testing, rather than dexamethasone suppression testing.⁷²

Surgical Treatment

Selective Adenomectomy

Successful adenomectomy eradicates the ACTH-secreting adenoma and immediately eliminates excess cortisol production while maintaining normal pituitary function (Fig. 5). Consequently, the initial treatment recommendation for CD is surgery.^{10,71} While some centers advocate medical therapy before surgery to reverse the effects of

FIG. 5. Surgical management of CD. **A:** Once a pituitary adenoma reaches a diameter of 3 mm, it compresses the immediately surrounding pituitary gland tissues to form a histological pseudocapsule comprising compressed pituitary gland and associated reticulin (*inset*). This histological feature creates a discrete tissue plane between the adenoma and normal pituitary gland that can be exploited to effectively resect small and large adenomas while minimizing injury to the surrounding pituitary gland. Several factors, including adenoma size, MR imaging findings, and dural invasion, impact the likelihood of surgical success in CD. **B:** The highest probability of successful resection (more than 95% of patients have biochemical remission) occurs in CD patients with adenomas that are large enough to create a peritumoral pseudocapsule, are visible on MR imaging (*top*) and do not invade the dural walls of a cavernous sinus. **C:** A number of CD cases are associated with adenomas that are not visible on MR imaging (*top*) and that are often small. When these tumors are large enough to form a histological pseudocapsule they can often be discovered through a series of incisions made sequentially deeper in the pituitary gland and successfully removed once they are visually identified (greater than 95% of patients in this circumstance have biochemical remission). Nevertheless, in some CD patients, an adenoma is not discovered after complete exploration of the pituitary gland, and partial (removal of 70%–80% of anterior pituitary gland or the half of pituitary gland that corresponds to increased ACTH levels during IPSS) or complete hypophysectomy is performed. Partial and complete hypophysectomy are associated with similar rates of biochemical remission (60%–80%) but complete hypophysectomy produces loss of pituitary function. **D:** When macroadenomas (1 cm or more in diameter) occur in CD patients, they are more often associated with dural invasion. In these cases, excision of the adenoma using the histological pseudocapsule is performed and the invaded dura is selectively removed. Copyright OSU Health Sciences Library Medical Visuals. Published with permission.

hypercortisolism, preoperative medical therapy complicates postoperative evaluation and is rarely necessary. Since 2010, surgical series generally show remission rates between 65% and 85% and recurrence rates of 10%–35% (Table 1).^{1–3,5,8,20,24,25,27,41,44,53,86,97,99,101,107} Surgical success and recurrence rates depend on surgeon experience, as well as the criteria used to define cure and length of follow-up.

Factors Affecting Surgical Outcome

Most of the emphasis on surgical technique for pituitary tumors over the past 30 years has been on approaches to the pituitary (sublabial, endonasal, endoscopic, and/or microscopic),⁶² instead of the details of how best to remove the tumor with most consistent success. Nevertheless, 3 factors influence the likelihood of successful surgery, including preoperative MR imaging findings, dural invasion by the adenoma, and adenoma size.

Preoperative MR Imaging Findings

Preoperative adenoma identification on MR imaging is associated with higher odds of finding the adenoma at surgery (18-fold higher) and postresection biochemical remission (4-fold).¹⁹ When an adenoma is seen on MR imaging, it directs surgical exploration to the adenoma location within the pituitary (86% correlation between MR imaging and surgical findings).¹¹⁰ A critical feature associated with successful surgical treatment, cavernous sinus dural invasion, is not well detected on MR imaging. Only 22% of cavernous sinus wall invasion cases in CD are accurately detected by MR imaging.⁵⁷

An MR imaging–invisible adenoma often can be found in CD patients by systematic exploration of the pituitary gland via a series of incisions carried deeper in stages.^{77,92} When adenomas reach a diameter of approximately 3 mm, a surrounding microscopic tissue envelope develops that corresponds to a rim of compressed gland adjacent to the edge of the adenoma (histological pseudocapsule) that can be used to identify small adenomas and that facilitates selective enucleation of both small and large adenomas.^{46,58,77} Selective adenomectomy using the histological pseudo-

capsule to define the boundaries of the adenoma achieves immediate and lasting remission in 97% of adult and 98% of pediatric CD patients.^{46,58}

Adenoma Dural Invasion

Persistent hypercortisolism after adenoma resection can result from dural invasion, which usually occurs laterally into the cavernous sinus wall. If dural invasion is limited to partial thickness invasion of the cavernous sinus wall, invaded portions of dura can be removed safely, resulting in biochemical remission.^{26,57} When the adenoma extends through the dural wall and invades the cavernous sinus, lasting curative surgery is unlikely, even with apparent complete removal of the tumor from the cavernous sinus.

Adenoma Size

When adenomas are so small that they cannot be located during pituitary gland exploration, a portion (partial hypophysectomy) or all (total hypophysectomy) of the anterior lobe may be removed. Partial hypophysectomy involves either removal of 70%–80% of the anterior pituitary lobe, leaving 20%–30% attached to the pituitary stalk, or removal of half of the anterior lobe corresponding to IPSS lateralization. Partial and total hypophysectomies have similar biochemical remission rates (60% to 80%) (Table 2).^{2,11,29,42,85,104} While partial hypophysectomy permits most patients to retain normal pituitary function, pituitary function is permanently abolished after total hypophysectomy.

Risks of Surgery

Risks of operative therapy for CD (2%–10% morbidity, less than 2% mortality) are similar to surgery for other pituitary tumors and include vision loss, other cranial nerve injury, vascular injury, loss of pituitary function, diabetes insipidus, delayed hemorrhage, and cerebrospinal fluid leakage.^{20,58,98} Because of the small size of most adenomas in CD, these risks occur less likely than after surgery for larger pituitary tumors.

TABLE 1. Surgical results for Cushing's disease based on recent reports*

Authors & Year	No. of Patients	Remission			Mean Follow-Up (yrs)	Recurrence
		Overall	Hypocortisolemic	Eucortisolemic		
Alahmadi et al., 2013	42	28 (67%)	22 (79%)	6 (21%)	2.8	7%
Alexandraki et al., 2013	124	84 (68%)	56 (45%)	28 (23%)	15.9	24%
Hameed et al., 2013	52	43 (83%)	13 (30%)	30 (70%)	1.4	14%
Lambert et al., 2013	257	230 (89%)	195 (76%)	NR	6.3	21%
Lonser et al., 2013	200	195 (98%)	189 (95%)	6 (3%)	6.8	7%
Starke et al., 2013	61	58 (95%)	35 (57%)	23 (38%)	2.3	11%
Wagenmakers et al., 2013	86	62 (72%)	NR	NR	5.9	16%
Aranda et al., 2015	32	32 (78%)	12 (38%)	20 (62%)	14.0	66%
Berker et al., 2013	90	81 (90%)	76 (94%)	5 (6%)	2.7	5.6%
Costenaro et al., 2014	103	84 (76%)	34 (40%)	NR	6	8%
Dimopoulou et al., 2014	120	85 (71%)	65 (76%)	20 (24%)	6.6	34%

NR = not reported.

* Adapted from Dallapiazza et al., 2015.

TABLE 2. Results for hypophysectomy for Cushing's disease

Authors & Year	No. of Patients	No Tumor Found	Total Hypophysectomy		Partial Hypophysectomy*	
			Patients	Remission	Patients	Remission
Tindall et al., 1990	52	13 (25%)	8	7 (82.5%)	5	5 (100%)
Bochicchio et al., 1995	668	NR	NR	(67%)	NR	(76%)
Hammer et al., 2004	289	62 (21%)	23	18 (78%)	25	23 (92%)
Esposito et al., 2006	40	9 (23%)	1	0 (0%)	8	4 (50%)
Pouratian et al., 2007	445	111 (25%)	28	14 (50%)	49	26 (53%)
Alexandraki et al., 2013	83	NR	26	15 (58%)	22	15 (68%)
Total	826	195 (24%)	86	54 (63%)	109	73 (67%)

* Hemihypophysectomy or partial hypophysectomy.

Absence of Hypocortisolism After Surgery

Within 48 hours of surgery, most patients in remission from CD develop a glucocorticoid withdrawal syndrome associated with circulating cortisol levels of 2 µg/dl or less (see *Measures of Biochemical Remission* below). Alternatively, with persistence of hypercortisolism after surgery, the source of the unsuccessful surgery must be residual tumor that was not removed. Four factors influence incomplete tumor removal: 1) the removal of incidental adenomas (which occur in 15%–20% of pituitaries at autopsy but for unexplained reasons are much less likely to occur during surgical exploration in CD) rather than the corticotroph tumor(s) can occur;⁵⁹ 2) mistakenly assuming an adenoma was found, resulting in the removal of a site that appears abnormal at surgery, but that proves to be normal gland on histological inspection; 3) incomplete removal of an ACTH-secreting adenoma contained within the pituitary; and 4) an invasive ACTH-secreting adenoma that was not recognized or incompletely removed at surgery can result in lack of biochemical remission.^{26,57}

The first 2 causes of incomplete ACTH-secreting adenoma removal often occur in patients when complete exploration of the gland was not performed after the apparent adenoma was removed (Fig. 6). Early repeat surgery is an option in these cases with exploration of the unexplored portion of the pituitary in an attempt to find and remove the adenoma, or removal of a portion of the remaining anterior lobe if no tumor can be identified, as described above. If an ACTH-staining adenoma contained completely within the pituitary gland was identified but only partially removed at the initial surgery, the residual tumor is always in the same region. Repeat surgery offers an excellent chance of complete resection in these cases. Thus, early repeat surgery has a reasonable chance of curing the condition and preserving pituitary function in the first three circumstances.^{9,88,95} On the other hand, if the gland was completely explored at the initial surgery by an experienced surgeon, the chances of achieving remission by finding and selectively excising an ACTH-producing adenoma are remote. Additional surgery is rarely indicated in this circumstance.

Recurrence of CD After Initial Surgical Remission

Delayed (months to years after initial biochemical remission) CD recurrence represents growth of residual microscopic tumor at the site, or immediately adjacent to

the adenoma resection site at the initial operation (Fig. 6). Similar to initial surgery, identification of recurrent adenoma on MR imaging guides surgery to the site of adenoma and predicts success of repeat surgery for recurrent CD.

Measures of Biochemical Remission

Determinates of lasting biochemical remission have not been defined. A variety of posttreatment criteria have been used to assess therapeutic success. Specifically, low (below 2 µg/dl) morning serum cortisol, low urine free cortisol levels (below 20 µg/24 hours), low serum ACTH (less than 5 pg/ml), and/or low midnight salivary cortisol within the 1st week have been used to predict lasting success.^{10,14,56,58} Recent data indicate that a morning serum cortisol level less than 1 µg/dl (on postoperative Day 3, 4, or 5 off of exogenous steroids) is the best predictor of lasting biochemical remission (96% positive predictive value). However, higher subnormal values do not exclude lasting remission. Dynamic testing, including CRH or desmopressin stimulation testing, can be used to predict biochemical remission but have not proven to be more effective in predicting long-term remission than basal serum cortisol levels.

Postsurgical Endocrinological Management

Hypocortisolism occurs after successful adenomectomy and reflects suppression of the normal pituitary corticotrophs by long-standing hypercortisolism. Typically, the suppressed normal pituitary gland corticotrophs in the hypothalamic-pituitary-adrenal axis typically do not recover normal function for 6–12 months. During this time, patients receive physiological glucocorticoid replacement (typically, hydrocortisone 10–12 mg/m² daily, given two-thirds in the morning and one-third in the afternoon). Restoration of hypothalamic-pituitary-adrenal axis function is assessed by return of normal morning cortisol levels (greater than 18 µg/dl) and/or a normal cortisol response to ACTH-stimulation. Hydrocortisone is then discontinued.

While the goal of adenoma resection is to preserve normal pituitary tissue and function, hypopituitarism occasionally occurs (less than 5%).^{20,58,85,92} Pituitary function is assessed within 2 weeks of surgery by measuring total T₄ and prolactin. If T₄ is similar to preoperative values and prolactin is greater than 4 ng/ml, the pituitary is considered functional. Characteristic CS-associated hypogonad-

FIG. 6. Management of CD in the absence of hypocortisolism after initial surgery (upper) and recurrence of CD after initial surgical remission (lower). **Upper:** Lack of biochemical remission after initial surgery is evaluated by early repeat pituitary MR imaging and detailed serial histological evaluation of specimens received from surgery. If MR imaging demonstrates an adenoma, early resection (within 3 weeks) directed by the imaging findings is performed. If ACTH staining is discovered on histological analysis, early resection directed by histological findings is performed. If MR imaging and histology findings are negative for evidence of CD, and hypophysectomy (partial or total) was not performed at initial surgery, then reexploration of the pituitary gland is performed. If hypophysectomy (partial or total) was performed at initial surgery, then adjuvant therapies are used to control CD. **Lower:** If recurrence of CD occurs after initial surgical remission, pituitary MR imaging is performed. If MR imaging reveals an adenoma that is resectable, surgery is performed to remove the adenoma. If the adenoma does not appear to be resectable on MR imaging, adjuvant therapy is used to control CD. If no adenoma is apparent on MR imaging, surgical exploration directed to the site of prior adenoma location is performed or adjuvant therapy is employed if features from prior surgery or patient condition preclude additional surgical exploration.

ism, relative hypothyroidism, and low growth hormone dynamics resolve slowly over 6–12 months. Treatment for these endocrinological changes is individualized according to patient age and symptoms.

Pathologic Findings

Harvey Cushing originally described the adenomas as-

sociated with CD as basophilic adenomas. Immunohistochemistry of CD adenomas shows diffuse ACTH-positive tumor cells. Because complete adenoma removal results in profound hypocortisolism (24–48 hours after surgery in most patients), it seems counterintuitive that the normal pituitary gland corticotrophs would retain normal ACTH-positive staining. Nevertheless, the normal gland corticotrophs do maintain ACTH-positive staining in CD.

At centers that infrequently deal with CD patients, ACTH-positive staining of the normal pituitary gland corticotrophs can occasionally lead to an incorrect diagnosis of diffuse corticotroph hyperplasia. In turn, this can lead to total hypophysectomy if it is not recognized as the normal pattern of staining in the normal gland in CD patients. In a series of more than 1500 patients with CD, we have not encountered a case of diffuse corticotroph hyperplasia in the absence of ectopic production of CRH (a very rare cause of CD that is associated with corticotroph hyperplasia).

In 75%–80% patients with chronic hypercortisolism of any etiology, the normal corticotrophs undergo changes in which the cytoplasmic granules are replaced with homogeneous hyaline material. These changes are histological changes known as Crooke's changes.⁷⁶ The presence of these changes is associated with the degree of hypercortisolism and individual susceptibility to them. The changes are never present in the absence of hypercortisolism. Consequently, their presence can be used to confirm that a patient in whom no signs of CS were seen on surgical exploration of the pituitary does, indeed, have CS. On the other hand, about 20% of patients with an ACTH-positive staining pituitary adenoma at surgery do not have Crooke's changes and, therefore, the absence of Crooke's changes does not establish the absence of CS.⁷⁶

Other Treatments

Medical Therapy

Medical therapy is the standard second-line treatment if surgery is not successful or if it is not possible. In these circumstances, medical therapy may be used adjunctively with radiation therapy to achieve eucortisolism while awaiting the therapeutic effects of radiation. Effectiveness of medical therapy (usually assessed by normalization of urine free cortisol levels) should be established before initiation of radiation treatment to avoid hypercortisolemia while waiting for the effects of radiation. Medical therapies include steroidogenesis inhibitors, corticotroph-directed agents, and glucocorticoid receptor blockers.

Steroidogenesis Inhibitors

Steroidogenesis inhibitors, mitotane, ketoconazole, metyrapone, and etomidate block one or more steps of adrenal steroidogenesis of cortisol. Mitotane is typically not a first-line agent because the high rate of gastrointestinal side effects, long onset to action, and its teratogenic/abortifacient effects in women who desire pregnancy. Recently, a large retrospective study (200 patients) revealed that 49% of CD patients treated with ketoconazole achieved normalization of urine free cortisol levels (an additional 26% of patients had a 50% or more decrease).¹⁵ Gastrointestinal side effects, inhibition of testosterone production, and hepatic dysfunction (and rarely death) occurred. Metyrapone has also been used to successfully treat CD patients.⁴⁷ Metyrapone has also been associated with gastrointestinal side effects and may exacerbate hypertension/hirsutism by blocking 21-hydroxylase and increasing precursors to cortisol that have mineralocorticoid and androgenic activity. As a result, ketoconazole may be better suited to women and metyrapone to men. Rarely, parental etomidate (anes-

thetic induction agent) was used in refractory cases to rapidly reduce supraphysiological cortisol levels but requires careful dose-titration.⁹¹

Corticotroph-Directed Agents

Pasireotide and cabergoline can inhibit ACTH production via binding to somatostatin and dopamine receptors expressed on corticotroph adenomas. Recently, pasireotide was found effective in reducing urine free cortisol levels (median 50% reduction) and associated clinical features.³² Common side effects included gastrointestinal symptoms, gallstones, and hyperglycemia.²³ The latter occurred in approximately 75% of patients and may limit this drug's use in patients with diabetes or glucose intolerance. Cabergoline reduces urine free cortisol levels in CD patients (40% partial and 35% complete response) but therapeutic escape occurs in 33% of patients after 6 to 18 months of treatment.⁸⁴ Treatment was well tolerated and hypotension was the only serious side effect (13%). Steroidogenesis inhibitors have also been combined with these corticotroph-directed agents (in short-term use) to elicit biochemical control in 90% of CD patients.

Glucocorticoid Receptor Antagonist

The glucocorticoid receptor antagonist mifepristone can be used to block the peripheral effects of elevated cortisol, including hyperglycemia. While a recent study indicates that mifepristone increases ACTH (2-fold) in CD patients, short-term imaging data suggest that CD-associated adenomas do not progress on treatment.³⁶ Because mifepristone increases ACTH and cortisol levels indirectly via peripheral glucocorticoid receptor blockade, there is no clear end point to follow regarding adequacy of the dose. Common side effects (nausea, fatigue, headache, and hypokalemia) are typically well tolerated and reversible,³⁵ but antiovarian and abortifacient effects may preclude use in women who desire pregnancy.

Radiation Therapy

Radiation therapy has been used for treatment of patients with CD for several decades. Radiation therapy was a mainstay of treatment when the source of CD was originally being elucidated. More recently, stereotactic radiosurgery (SRS) approaches (i.e., Gamma Knife, linear accelerator, proton beam) that precisely target the region of treatment have been introduced. The optimal dose is 20–25 Gy for SRS and 45–50.4 Gy given over 5 weeks for radiation therapy.^{85,98} Generally, the incidence of remission in CD seems to be similar between the various forms of radiosurgery (43%–58%) and fractionated therapies (46%–84%; Table 3),^{13,30,85,94,98,108,109} but the pace of the therapeutic response may be faster with SRS. The major risk of SRS or fractionated irradiation therapy is loss of pituitary function, which is presumably the net effect of surgery and radiation. Loss of pituitary function occurs in about 20%–40% of patients at 10 years after radiation therapy and increases thereafter. The principal advantage of the SRS approaches over fractionated radiation methods is that they can be delivered in one session of therapy, rather than over several weeks.

TABLE 3. Radiation results for Cushing's disease based on recent reports

Authors & Year	Technique	No. of Patients	Follow-Up (yrs)	Margin Dose (Gy)	Biochemical Remission
Sheehan et al., 2013	Gamma Knife	96	48	22	70%
Wattson et al., 2014	Proton beam	74	52	20	54%
Wilson et al., 2014	Linear accelerator	36	66	20	22%
Budyal et al., 2014	Fractionated	20	48	45 (25 fractions)	75%

Adrenalectomy

Because the adrenal cortices are the target organs of ACTH and the source of supraphysiological cortisol secretion in CD, bilateral adrenalectomy can be used to treat refractory cases of CD. Adrenalectomy is typically performed laparoscopically and produces biochemical remission in greater than 95% of refractory cases of CD. Bilateral adrenalectomy is associated with an 18% median morbidity rate within 30 days of surgery. There is a 28% median rate of adrenal crisis after bilateral adrenalectomy. Mortality associated with bilateral adrenalectomy has been estimated at 9% and is most frequently due to stroke and myocardial infarction.⁹⁰

There is a 21% median rate of Nelson's syndrome (pituitary adenoma progression with progressive elevation of ACTH due to lack of cortisol negative feedback) after bilateral adrenalectomy.^{67,68,90} Early data suggest the incidence and severity of Nelson's syndrome is minimized by precedent postoperative (after pituitary surgery) radiation.^{48,63} Nelson's syndrome can be treated by observation (for stable small tumors), tumor resection, tumor/sella radiation, and/or pharmacotherapy. Typically, resection of pituitary adenoma or hypophysectomy is the treatment of choice. If surgery is ineffective or not possible, tumor/sella radiotherapy or radiosurgery can be performed. Finally, pharmacotherapy is used as an adjunct to treat Nelson's syndrome.⁷⁹

Conclusions

Increased understanding and improved diagnostic paradigms have enhanced detection and diagnosis of CD. Today, most CD patients can be cured by surgery or successfully managed by surgery combined with adjuvant therapies.

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Disclosures

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Author Contributions

Conception and design: Lonser, Oldfield. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lonser. Administrative/technical/material support: Lonser, Oldfield. Study supervision: all authors.

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