Chapter 14
Surgical Management of Hypercortisolism from ACTH-Secreting Pituitary Adenomas

Justin C. Morse, Brian D. Thorp, and Adam J. Kimple

Introduction

Cushing syndrome (CS) is the constellation of findings that are noted from prolonged exposure to glucocorticoids. Typical findings include obesity, hypertension, diabetes mellitus, and osteoporosis. CS may result from multiple causes including immunosuppression with corticosteroids and adrenal tumors or form Cushing's disease. Cushing's disease (CD) results from a benign monomorphic pituitary corticotroph adenoma that secretes excessive adrenocorticotropic hormone (ACTH). Increased ACTH stimulates secretion of cortisol by the adrenal glands, resulting in supraphysiological levels of endogenous steroid resulting in the combination of symptomatology and findings characteristic of CS.

CD is rare with an incidence estimated at one to two per million which limits large studies of these patients [1]. These tumors remain challenging to treat for both the surgeon and endocrinologist. Transsphenoidal adenomectomy (TSS) remains the treatment of choice for the vast majority of patients with the concurrent goals of biochemical remission and maintenance of pituitary function; however, remission rates after TSS range from 65% to 80% [2, 3]. Unsuccessful treatment results in reduced quality of life and increased mortality [4]. This chapter seeks to (1) discuss the preoperative planning for surgical resection of ACTH-secreting pituitary adenomas, (2) describe the endoscopic surgical technique for transsphenoidal resection of sellar tumors, and (3) discuss the postoperative care of patients after resection of an ACTH-secreting pituitary adenoma. For readers interested in a nuanced discussion

J. C. Morse · B. D. Thorp · A. J. Kimple (✉)
Department of Otolaryngology-Head and Neck Surgery, University of North Carolina Medical Center, Chapel Hill, NC, USA
e-mail: adam_kimple@med.unc.edu

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of the pros and cons of different surgical and reconstructive techniques, we recommend the text by Drs. Snyderman and Gardner entitled *Master Techniques in Otolaryngology – Head and Neck Surgery: Skull Base Surgery* [5].

Diagnosis and Preoperative Planning

Patients with suspected CD presenting to a surgeon have usually already undergone an extensive diagnostic workup including demonstration of elevated ACTH and cortisol in combination with imaging evidence of a pituitary adenoma. However, several diagnostic dilemmas exist that deserve special attention. ACTH-secreting pituitary tumors are often discovered when they are quite small because of their potent biological/clinical effects. In fact, large case series indicate that over 90% of ACTH adenomas are microadenomas with a mean diameter of 6 mm at the time of diagnosis [6, 7]. As such it is not uncommon to have negative imaging or discordant biochemical and radiological studies leading to diagnostic uncertainty. Furthermore, the small size and the lack of contrast between the adenoma and the surrounding pituitary gland result in a negative magnetic resonance imaging (MRI) scan nearly 50% of the time at diagnosis. New imaging techniques have sought to improve visualization of these small lesions, and some have advocated for spoiled gradient recalled (SPGR) acquisition MRI sequences. This imaging sequence has been suggested to increase identification of adenomas to 65–80% at the time of diagnosis [8, 9].

Unfortunately, even with advanced imaging techniques, negative imaging remains relatively common. Moreover, peripheral ACTH levels can be nondiagnostic or discordant. To address these issues, inferior petrosal sinus venous sampling (IPSS) has been advocated to help confirm a diagnosis and has been reported to help localize laterality of the tumor at some centers [10, 11]. IPSS is based on anatomic venous drainage of the pituitary gland which occurs laterally into the cavernous sinuses and subsequently into the inferior petrosal sinuses. The short half-life of ACTH leads to an ACTH concentration difference between the inferior petrosal veins and the peripheral blood. As such, more concentrated blood can be sampled from the direct venous drainage of the pituitary compared with sampling from the systemic venous system. Furthermore, corticotropin-releasing hormone (CRH) stimulation during inferior petrosal sinus sampling allows for improved diagnostic confirmation of an ACTH adenoma [12]. Because cavernous sinus blood generally enters the petrosal venous system unilaterally, bilateral sampling is recommended [10]. Furthermore, because of the frequent ipsilateral lateralization of the 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 [10, 13]. It is important to note that in order 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 leading to an inferior petrosal sinus-to-peripheral ACTH gradient suggestive of CD, when in fact

it should be normal [14]. While IPSS remains a successful tool in the diagnosis of CD, its success remains quite operator dependent and varies substantially from center to center [11, 15]. Ultimately IPPS has a diagnostic accuracy around 95% in institutions with broad experience [11, 14, 16].

Indications for IPSS vary between centers; however, most institutions with expertise in CS use this technique only in patients with ACTH-dependent CD that has conflicting results of noninvasive endocrine evaluation, discordant biochemical and radiological studies, or negative pituitary MR imaging [6].

Once the diagnosis is confirmed, further preoperative planning for any suspected pituitary tumor including those with ACTH secretion is approached in a similar fashion. A multidisciplinary approach remains paramount to achieving a successful surgical outcome. While imaging has been obtained for the identification of tumor location, separate imaging should be performed for preoperative planning to be utilized with intraoperative image guidance systems. Specifically, thin-slice MRI with and without contrast as well as thin-slice (~0.6 mm) computed tomography of the sinuses provides adequate visualization of the surrounding anatomic structures and tumor location while further allowing utilization of image guidance surgical systems. Preoperative pituitary hormone labs including cortisol, TSH, IGF-1, and prolactin are drawn for baseline values if not already obtained.

Indications and Contraindications

Apart from prolactinomas and a subset of growth hormone-secreting tumors, surgery remains the first-line therapy for pituitary tumors, including ACTH-secreting adenomas [17]. Few surgical contraindications exist and can be generalized as comorbidities preventing safe administration of anesthesia or increased risk of surgical bleeding. These include but are not limited to bleeding diatheses or anticoagulation that cannot be safely stopped, uncontrolled hypertension, or significant comorbidities that increase anesthetic risk to the point that risks of surgery outweigh any potential benefit. Reducing intraoperative and postoperative bleeding risk is particularly important in these cases as hematoma development can result in significant morbidity including rapid vision loss, seizures, or other neurologic decline.

Surgical Technique

The origins of pituitary surgery have been reported as early as the seventeenth century [18]. Modern resection of sellar masses is usually accomplished via the transnasal approach as opposed to transcranial or transfacial approaches. Historically these transnasal approaches were performed with a microscope, but contemporary management generally consists of endoscopic transnasal resection [6]. Equivalency of the transnasal endoscopic approach compared to the transnasal microscopic

approach is well documented [19]. Furthermore, current evidence appears to favor the endoscopic approach for multiple reasons including improved visualization and improved access and some reports detailing improved resection outcomes/lower recurrences [20]. ACTH-secreting pituitary adenomas are effectively managed with endoscopic techniques, and the authors herein describe this surgical approach.

Approach

An understanding of endoscopic transsphenoidal surgical resection of sellar tumors including ACTH-secreting tumors relies on an intricate understanding of both nasal and sellar anatomy. We describe a brief overview of the endoscopic/intranasal anatomic landmarks utilized for this approach and the surgical technique. Resection of these tumors remains a team-based approach with both the otolaryngologist, specifically those subspecializing in rhinology and endoscopic skull base surgery, and a neurosurgeon. We will focus specifically on two key components of this surgery: (1) the intranasal approach and (2) the sella and its corresponding anatomy to a transsphenoidal approach for resection of an ACTH adenoma.

The intranasal cavity is the space between the vestibule of the nose and the choanae. The nasal passages are separated in the midline by the nasal septum. This passageway provides access to several adjacent corridors including the surrounding sinuses, anterior, middle, and posterior cranial fossa, craniocervical junction, and the sella.

Herein we describe an overview of the endoscopic approach to the sella. A 0-degree endoscope is utilized to perform nasal endoscopy. The middle turbinates are lateralized or removed thereby allowing visualization and access to the sphenoethmoidal recess and superior turbinate. The inferior 1/3 of the superior turbinate is removed with cutting instrumentation allowing visualization of the natural os of the sphenoid sinus which is medial to the superior turbinate approximately 1.5–2 cm from the superior aspect of the choanae. If a nasoseptal flap reconstruction is planned, the flap is raised at this point in the surgery and placed into the nasopharynx (see sellar reconstruction techniques below). The os is entered and widened to the planum of the sphenoid bone superiorly and laterally to the orbital apex (Fig. 14.1). Opening of posterior ethmoid cells increases visualization. If a nasal septal flap or rescue flap is going to be used for reconstruction, the inferior mucoperiosteum of the sphenoid face must be preserved to avoid injury of the posterior septal branch of the sphenopalatine artery which courses 1 cm superior above the top of the choanae and is the vascular pedicle for the nasoseptal flap that remains the main workhorse for reconstruction.

With the skull base identified on one side, a superior septectomy of the posterior nasal septum is performed to allow access to the contralateral sphenoid os. Bilateral sphenoid access is obtained, and the contralateral face of the sphenoid is opened resulting in a common sphenoid cavity. At this point the sphenoid intersinus septum

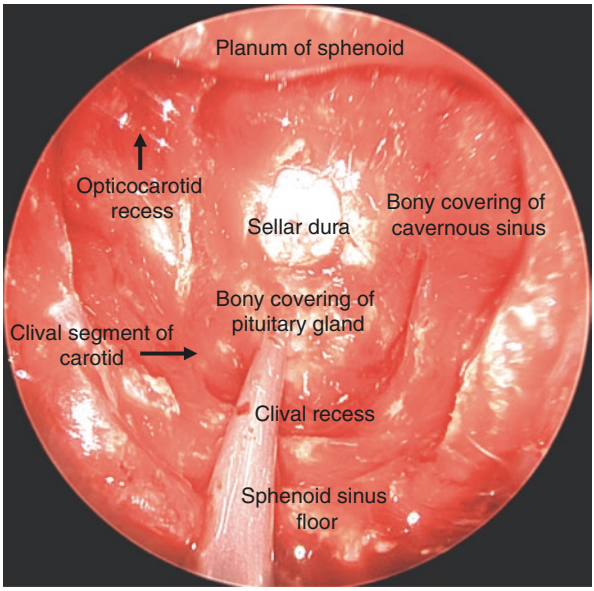

Fig. 14.1 Endoscopic transsphenoidal visualization of the sella and labeled osteologic landmarks prior to the opening of sella dura for resection of ACTH-secreting adenoma

is removed allowing wide visualization of the sellar osteology. Visualization of the clival recess, sella, clival carotids, and lateral opticocarotid recesses is important prior to performing any osteotomy (Fig. 14.1). With the surrounding anatomy visualized, an osteotomy of the anterior face of the sella is performed to expose the dura of the anterior pituitary gland. This exposure allows for transnasal instrumentation and easy visualization of the surrounding anatomy to facilitate a safe tumor resection.

Tumor Resection

Tumor resection requires a complete understanding of the sellar and parasellar regions. This is a complex anatomic region that contains critical neurovascular structures. A midline durotomy allows visualization of the tumor and pituitary gland. Care should be taken to avoid entering the cavernous sinus. At times, a pseudocapsule surrounding the tumor can allow an extracapsular dissection, particularly in ACTH-secreting tumors. A combination of curettes, suction, and grasping instruments is used to remove the adenoma. Direct transsellar endoscopic visualization facilitates gross total resection. In the setting of lateral dural invasion, the dura of the cavernous sinus wall can be resected for removal of the entirety of an invasive tumor. Further dissection may need to occur into the retro cavernous carotid space as this is a common area for tumor to be missed. Once tumor resection is complete, attention is turned toward the reconstruction of the skull base/sellar defect.

Skull Base/Sellar Repair

While the nuances of skull base reconstruction are outside the scope of this chapter, it is important to understand the two primary goals of sellar reconstruction: (1) separating the intranasal cavity from the intracranial cavity for prevention of infection and (2) preventing or stopping CSF extravasation. Sellar reconstruction can broadly be thought of in two scenarios: (1) no intraoperative CSF leak and (2) with an intraoperative CSF leak. Intraoperative CSF leaks can be classified as low-flow (not originating from a CSF basin) and high-flow leaks (originating from a cisternal space). The reconstruction of high-flow CSF leaks has higher complication rates [21] and generally warrants a multilayer repair including an inlay graft and a vascularized onlay nasoseptal flap. ACTH-secreting tumors have been shown to have higher complication rates than non-secreting pituitary adenomas [6], and we generally advocate for a more robust reconstruction, such as the nasoseptal flap. If no leak is encountered, reconstruction techniques are highly variable and surgeon dependent. Several common reconstruction practices include abdominal fat graft [22], synthetic dural inlay, an overlay mucosal graft, pedicled flap, or dissolvable packing material alone [23].

Surgical Challenges

For ACTH-secreting pituitary adenomas, surgery can be complicated by negative preoperative imaging, small adenoma size, complicating intraoperative localization, or dural invasion. Preoperative identification of the tumor results in increased chances of intraoperative identification and postoperative biochemical remission [24]. If not identified preoperatively on MRI, systematic exploration of the pituitary gland is often efficacious in identifying the tumor [25]. Interestingly, adenomas of ~3 mm or greater often develop a surrounding microscopic pseudocapsule that can be used for tumor identification and facilitate selective enucleation [25, 26]. When applicable, selective adenomectomy using the histological pseudocapsule to define the boundaries achieves immediate and lasting remission in the majority of both adult and pediatric CD patients [7].

When adenomas cannot be identified, a partial hypophysectomy or total hypophysectomy may be performed. 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 with the clear advantage of partial hypophysectomy as it allows most patients to retain normal pituitary function and not require lifelong pituitary supplementation [27].

Dural invasion can result in non-curative outcomes. 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 [28]. Unfortunately, if the adenoma extends through the dural wall leading to

subsequent cavernous sinus invasion, surgery is unlikely to be curative, even with gross total removal of the tumor from the cavernous sinus [7].

Postoperative Care

Postoperative care varies between institutions; however, in patients with CD, we advocate for at least 24 h in the neurointensive care unit postoperatively. This allows improved management of blood pressure and glucose. Urine output and osmolarity are assessed for diabetes insipidus. In our practice, a lumbar drain is not routinely utilized. Postoperative cortisol is measured on postoperative day 2 to confirm successful resection. Nasal saline sprays are initiated on postoperative day 1, and nasal saline irrigations are typically initiated after the first postoperative appointment. During the surgical admission, a postsurgical MRI is obtained to serve as a new baseline. Clinical follow-up is scheduled with otolaryngology at 1, 4, and 12 weeks postoperatively for nasal debridement. Neurosurgical follow-up is recommended at approximately 1 month postoperatively and endocrinology follow-up at 1–2 weeks. Continuous positive airway pressure is avoided for 4 weeks following surgery.

Postsurgical endocrinological management deserves special attention. A successful surgery results in postoperative hypocortisolism secondary to suppression of the normal pituitary corticotrophs by long-standing hypercortisolism. Recovery of the suppressed normal pituitary gland corticotrophs occurs over 6–12 months. During recovery, it is crucial that patients receive physiological glucocorticoid replacement. Restoration of function of the hypothalamic-pituitary-adrenal axis is confirmed with a normal morning cortisol level and/or a normal cortisol response to ACTH stimulation. At this point, steroid supplementation is discontinued.

While the goal of adenoma resection is to preserve normal pituitary tissue and function, hypopituitarism occurs approximately 5% of the time [7, 27, 29]. Management of postoperative hypopituitarism includes pituitary functional assessment with T4 and prolactin measurements 2 weeks after surgery. The pituitary is considered functional if preoperative T4 and postoperative T4 are similar, and prolactin is greater than 4 ng/ml. Treatment for CS-associated hypogonadism, relative hypothyroidism, and low growth hormone is individualized to the patient and is expected to resolve gradually over 6–12 months.

Surgical Complications, Unsuccessful Surgical Resection, and Non-remission

Morbidity from transsphenoidal surgery has been estimated at 2–10% and mortality at <2% which align with the rates seen in all pituitary surgery [29]. Complications from surgery can broadly be divided into (1) rhinologic, (2) neurologic, and (3) endocrinologic.

Rhinologic complications include intranasal bleeding and infection. Postoperative bleeding is rare and with a reported incidence of 0.6–3.3% [30]. In most cases, postoperative bleeding can be stopped with the use of an intranasal hemostatic agents and/or a vasoconstrictive nasal spray such as oxymetazoline. Bleeding refractory to medical management or high-volume hemorrhage requires endoscopic control in the operating room. The most severe form of postoperative infection is meningitis, and it is estimated to occur <1% of the time [19, 31, 32]. Culture-directed antibiotics are the primary treatment.

Neurologic complications include intraoperative damage to surrounding structures and postoperative CSF leak. Management of postoperative leak can be managed using either with a revision skull base reconstruction or more conservative methods depending on surgeon preference. Initial treatment with CSF diversion using a lumbar drain can be successful [21]. If CSF extravasation persists despite a lumbar drain, head of bed elevation and bed rest and additional surgical repair are required. Additionally, neurologic complications primarily include carotid injury, vision loss, or stroke [31].

Finally, endocrinologic complications result from manipulation and/or resection of the normal pituitary gland. As discussed above, postoperative pan-hypopituitarism occurs in <5% of patients. Berker et al. report endocrinologic complication rates of 570 pituitary adenomas with a rate of transient diabetes insipidus (DI) of 4.6%, permanent DI in 0.4%, and inappropriate antidiuretic hormone secretion syndrome occurred in 1.1% [6, 31].

Unsuccessful surgical resection is suspected in the absence of hypocortisolism postoperatively. Most patients in remission from CD develop a glucocorticoid withdrawal syndrome within 48 h of resection. Lonser et al. describe several reasons that influence incomplete tumor removal: (1) the removal of an incidental adenomas rather than the actual corticotroph tumor [33], (2) the removal of a site that appears abnormal at surgery but proves to be a normal gland on histological inspection, and (3) the incomplete removal of an ACTH-secreting adenoma due to inadequate resection or invasion into surrounding structures [6, 7].

When the actual tumor is not resected, revision surgery can be attempted to remove the adenoma or remove additional anterior pituitary gland if no tumor is identifiable. If pathology from the initial surgery demonstrates an ACTH-staining adenoma, repeat surgery offers an excellent chance of complete resection [6, 34]. It is important to note that if the gland is completely explored at the initial surgery or there is invasion into the cavernous sinus, achieving remission with a revision surgery is unlikely [6]. As such, medical therapy remains second-line treatment in the scenario of unsuccessful surgery or when surgery cannot be performed. Medical therapies include steroidogenesis inhibitors, corticotroph-directed agents, and glucocorticoid receptor blockers [6]. Discussion of the use of each of these therapies is outside of the scope of this chapter.

Another adjuvant treatment in the setting of unsuccessful surgical remission is radiation therapy and can include either stereotactic radiosurgery or standard fractionated irradiation [27, 35, 36]. Studies have demonstrated that both

modalities are equally efficacious in treating CD [27, 36, 37]. The major risk with radiation therapy is long-term pituitary hypofunction with reported rates of up to 40% 10 years posttreatment [36].

Conclusion

ACTH-secreting pituitary tumors resulting in CD are generally small. Diagnosis relies on imaging and lab workup. While diagnostic challenges exist, IPSS has significantly improved the ability of confirmatory diagnosis and can assist with localization of tumors not seen on imaging. Surgical management via an endonasal transsphenoidal approach of ACTH-secreting pituitary adenomas resulting in CD remains first-line therapy with excellent success at experienced centers. Surgical complications are rare. The goals of surgery remain gross total resection resulting in biochemical remission of hypercortisolism with simultaneous maintenance of pituitary function. Non-remission remains a challenge, and options to treat this include revision surgery, medical therapies, and radiation therapy.

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