CHAPTER 3

Strategies for the Management of Nonsecreting Pituitary Adenomas

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The two objectives of treating pituitary tumors are: (1) relief of signs and symptoms attributable to mass effect, and (2) correction of hypo- or hypersecretion of adenohypophyseal hormones.[7] When nonsecreting tumors are specifically considered, correction of endocrine abnormalities may be of less consequence than hormonal excess, but continued growth of the lesion may precipitate hypopituitarism.

Radioimmunoassay has revolutionized the diagnosis and management of pituitary tumors. Complementary immunocytochemical methods have rendered original morphometric histological classification methods of pituitary tumors clinically obsolete. In conjunction with advances in radiographic imaging and electron microscopy, the detection, diagnosis, and definition of these lesions have been greatly enhanced and our understanding of the nature of the production and discharge of pituitary hormones has been extended.[4]

Clinical and Endocrinological Diagnosis

Compared to hormonally active tumors, nonfunctioning pituitary adenomas more frequently present with symptoms of tumor mass effect, such as headache, visual failure, or hypopituitarism. Null cell tumors are statistically the most common type of adenoma found in the pituitary, and present more frequently later in life than secreting tumors. The classic visual triad produced by larger tumors is characterized by optic disc pallor, early loss of central visual acuity, and visual field defects (bitemporal hemianopsia).[41]

Nonsecreting pituitary adenomas may be defined as those that are apparently inactive clinically and biochemically. Apparent inactivity does not rule out the potential for secretion of an as-yet undetectable hormone or its precursor, or the synthesis of a known hormone in insufficient quantities to be detected by immunoperoxidase methods.[22] Indeed, the term "nonfunctioning" has been considered by some a misnomer for this reason.[1]

In the patient suspected of harboring a nonsecreting tumor, one must be aware that larger tumors may cause a mild to moderate hyperprolactinemia resulting from the so-called "stalk-section effect." This disconnection hyperprolactinemia—stalk compression causing loss of dopaminergic inhibition to tonic prolactin release—must be distinguished from a true prolactinoma.[27]

Under such circumstances, it is rare to see prolactin levels in excess of 100 ng/ml, at most 150 ng/ml. Consequently, large tumors (>2 cm in size) associated with prolactin levels of <150 ng/ml, and certainly those of <100 ng/ml, should be considered to be nonsecretors when planning management strategies. In particular one must be cautious in expecting such lesions to diminish in size

in response to dopaminergic agonists such as bromocriptine. Aside from mild elaboration of prolactin as a result of "stalk-section effect," these tumors are characterized by no clinical or biochemical abnormality indicating hormonal excess.[21]

To be distinguished from the true nonfunctioning tumors are those that secrete the alpha-subunit, common to all of the glycoprotein hormones. The alpha-subunit may be detected immunohistochemically in tumor specimens and biochemically in the urine; but, as it possesses no biological activity, its secretion has no endocrinological consequence.

The exclusive secretion of the alpha-subunit may be difficult to determine if each of the glycoprotein hormones has not been independently assayed. For example, thyroid-stimulating hormone (TSH) secreting tumors may secrete excessive quantities of the alpha-subunit.[34]

Because these tumors are often quite large at the time of presentation, varying amounts of hypopituitarism may be present. This occurs because normal functioning glandular tissue is compressed by the tumor, or because of interference with blood supply, leading to infarction of normal functioning gland. Reports of reversibility of hypopituitarism following surgical decompression indicates the possibility for interruption of the hypothalamic-portal pituitary circulation without true necrosis of glandular tissue.[2,29]

Surgical Approach

The transnasal transsphenoidal approach is currently considered the procedure of choice for surgical access to sellar lesions. The first successful transnasal approach to a pituitary adenoma was described in 1907 by Schloffer, an Austrian rhinologist.[32] His approach was adopted and modified by other European surgeons, and by Cushing in the United States, who introduced the sublabial incision. Original high morbidity of the procedure resulted largely from meningitis and the unavailability of synthetic glucocorticoids to supplement patients with lack of pituitary reserve during the perioperative period. This led to a waning of interest in its use.

Resurgence of interest in the transsphenoidal approach was popularized by Guiot[16] and Hardy,[17] who further refined it by the introduction of the operating microscope and fluoroscopic monitoring. Increased use of this technique may also be attributed to the well-recognized inadequacy of the subfrontal approach to achieve removal of the intrasellar component of the tumor. Several reports have demonstrated the inherent benefit of the transsphenoidal approach in the primary surgical management of these lesions.[10,12,17,18] Favorable results of the transsphenoidal approach also have been reported in the management of visual disturbances from macroadenomas,[9,11,41] establishing this as the approach of choice for the surgical management of most pituitary tumors, regardless of size.

From among 1,000 patients with pituitary lesions who were operated on via the transnasal transsphenoidal route, we assessed more than 200 who presented with visual loss. Our assessment yielded evidence of improved vision in 81%, unchanged vision in 16%, and worsening of vision in 3%. These results are similar to those reported in other large series concerning the efficacy of the transsphenoidal approach to suprasellar tumors. Visual outcome after the transsphenoidal approach is equal or superior to the results reported in large series of subfrontal explorations for visual loss.

Clear documentation exists for the potential improvement in pituitary function following transsphenoidal adenomectomy with careful preservation of normal gland in cases with preexisting hypopituitarism.[2,29] The efficacy of transsphenoidal surgery in selected patients with microadenomas has been established, with some reports of greater than 90% tumor control.[30,35] In series including larger tumors, however, a less optimistic 50-85% tumor control has been reported with surgery alone.[8,9,31]

Transsphenoidal microsurgery for both large and small adenomas has acceptable mortality and morbidity when done by experienced surgeons.[5] Of 2,606 microadenomas and 2,677 macroadenomas reported in the international survey by Zervas,[42] the death rate was 0.27% and 0.86%, respectively. Direct injury to the hypothalamus seemed to be the major cause of surgical death, with delayed mortality attributed to fistula and meningitis, or as a result of vascular injury.

Operative morbidity includes persistent or permanent diabetes insipidus (DI), the incidence ranging from 1.8% permanent DI in the 505 cases reported by Laws and Kern[26] to a 17% incidence immediately postoperatively with large adenomas as reported by Cohen.[11] Postoperative CSF fistulas range from 1.0% to 4.4% in different series,[13,40] depending upon the size of the lesion and follow-up time, but they occur disproportionately with larger lesions.[5]

Of more than 1,500 cases reviewed at the Mayo Clinic by Laws,[24] major morbidity (stroke, visual loss, vascular injury, meningitis, CSF rhinorrhea, cranial nerve palsy) was encountered in 3.5%, and minor morbidity (bleeding, nasal or sinus problems, DI, SIADH, transient cranial nerve paresis, transient psychosis) occurred in another 3.5% of patients. Complications amount to a relatively small percentage of the overall surgical experience, emphasizing the relative safety of the procedure.

The rare contraindications to the transsphenoidal approach include: (1) extensive lateral tumor growing into the middle fossa with minimal midline mass; (2) ectatic carotid arteries projecting to the midline; and (3) acute sinusitis, which may delay the procedure for treatment of the infection. Previous rhinoplasty or submucous resection may increase the difficulty of the dissection planes, but this should not constitute a contraindication to the transnasal approach.

Tumor extension into the middle fossa requires careful inspection of imaging evidence regarding the precise location of such lateral extension. In patients who have not had previous surgery, our experience has been that such lesions gain access to the middle fossa by extension through the cavernous sinus. Many of these "middle fossa extension" lesions remain within the confines of the cavernous sinus and extend into the middle fossa by ballooning the lateral wall of the cavernous sinus. The optimal approach is transsphenoidal, following the extension of the tumor into the cavernous sinus from either the sphenoid sinus or, more commonly, the sella turcica.

A detailed description of the transnasal transsphenoidal procedure performed at our institution has been published elsewhere.[38] In those aspects of the procedure that specifically pertain to large pituitary tumors, exposure is critical. This is especially true in intrasellar exposure, due to the long operative corridor and relatively small sellar target. Adequate bony removal is essential to obtain complete sellar access. The location of the carotid arteries on the coronal MRI should be noted, as this information is valuable when opening the dura at the lateral margins of the sella.

Characteristically, these tumors are soft and friable, and at surgery may herniate down through the diaphragma sellae after evacuation of the intrasellar component; this may be facilitated by asking the anesthetist to perform a Valsalva maneuver intraoperatively. Other techniques to promote herniation include the infusion of air or saline through a previously placed cisternal or lumbar catheter.[1,39]

A pure suprasellar tumor, or one that requires suprasellar access may be approached, if necessary, by carrying the bony resection anterior over the tuberculum sella with exposure of the dura mater lying anterior to the circular sinus. A transverse incision may be then made in the dura rostral and caudal to the circular sinus, with bipolar coagulation and transection of the circular sinus, an intradural structure contained between the leaves of the dura. Transection of the circular sinus will then enable exposure of the suprasellar cistern itself, and provide adequate room for

surgical resection of tumor in this location.

Once the mass has been resected, attention must be paid to obliteration of the CSF fistula if the arachnoid has been violated. As early as 1952, Hirsch[19] fully recognized the limitations of any intracranial attempt to control the leak, as he reported the first successful attempt to close a sphenoidal leak following hypophysectomy using a septal mucoperichondrial flap.

During transsphenoidal procedures in which the arachnoid has been breached, we routinely harvest a fascia lata graft of appropriate size to cover the opening. The graft is placed on the intradural side of the opening, within the intrasellar compartment, and a small piece of Marlex mesh is fashioned and placed within the sella to maintain the apposition of the fascial graft. Placement of the fascial graft is critical, as the intracranial pressure will tamponade the graft to the dura if properly inserted.

Prior to closing, the anesthetist is asked to perform a Valsalva maneuver to assess the functional integrity of the graft. The sphenoid sinus behind the graft is then packed with fat obtained at the harvest of the fascial graft to further buttress the graft in position. If no CSF leakage is seen around the graft, the retractor is removed, and the posterior nasal pack is placed against the sphenoidal opening. We then perform a lumbar puncture with an 18-gauge needle in the recovery room and on the first postoperative day to further decrease the chances of a persistent fistula developing.

In the unusual event that a postoperative leak occurs following this protocol, an early return is made to the operating room for formal repacking to avoid meningitis. Little is to be gained by waiting in these cases as the relatively avascular graft is less likely to close spontaneously than in the posttraumatic situation. We routinely obtain nasopharyngeal cultures prior to prepping of the nose to guide antibiotic coverage should postoperative meningitis occur.

The remarkably low morbidity and mortality associated with transsphenoidal resection of even very large tumors has encouraged our group to consider this approach as the preferred primary means of resecting almost all macroadenomas. Many tumors will herniate into the enlarged sella from the suprasellar cistern, subfrontal space, and cavernous sinus once the intrasellar component has been evacuated. We have, on rare occasions, found tumors that do not enlarge the sella but grow directly into the suprasellar cistern. These may present a particular problem; but, by mobilizing normal gland and opening through the tuberculum sellae as described above, one can frequently gain access to the suprasellar cistern and extract the tumor.

Perioperative Management

Perioperative glucocorticoids should be administered to all patients. This is particularly important if preoperative endocrine assessment indicates any hypocortisolemia. We routinely administer methylprednisolone 40 mg Q6H or dexamethasone 10 mg Q6H in the perioperative period in those cases with visual compromise. Medication is usually started the day prior to surgery and continues for 1 to 2 days postoperatively; a tapering dose is tailored to the individual patient's projected glucocorticoid needs by the preoperative endocrine assessment and intraoperative findings. In those cases without visual compromise, lower dosages of these high-potency glucocorticoids with a more rapid postoperative taper may be employed.

Thyroid function should be assessed preoperatively, and the patient treated to restore the euthyroid state prior to elective surgical intervention. The stress of surgery may provoke an acute crisis in the patient without sufficient reserve; hypothyroidism should be a consideration in patients with an otherwise unexplained alteration in postoperative mental status.

We have abandoned the routine use of perioperative antibiotics. The liberal use of bacitracin-impregnated irrigant has been sufficient, in our experience, to prevent infec-

tion. Nevertheless, the transsphenoidal route should be considered only semi-sterile. In the advent of postoperative meningitis, therapy must begin with antiobiotics to cover colonizing organisms identified from the routine preoperative nasopharyngeal culture.

Serial visual field testing is routinely performed in the recovery room and intensive care unit to monitor visual function. In the patient with preoperative visual deficit, careful monitoring in the early postoperative period is essential. Both the transfrontal and transsphenoidal routes are successful in improving vision.[9,15,40] Immediate postoperative improvement of vision may occur,[14] with a significant improvement usually within the first 2 weeks, although continued improvement may occur for up to 12 months.[20]

More importantly, any loss of vision in the postoperative period may indicate an evolving hemorrhagic complication that may be diagnosed by CT scanning. Progressive visual deficit with postoperative hematoma in the tumor bed would warrant reexploration. Early postoperative scanning, both CT and MR, may demonstrate false evidence of suprasellar hemorrhage due to postoperative changes that give the spurious impression of a suprasellar hematoma. Consequently, the clinical evidence provided by progressive visual loss remains the primary guide to the need for reexploration, supplemented by imaging evidence.

Blood pressure is carefully monitored. Hypotensive events must be avoided, especially in patients in whom tissue perfusion is already marginal. We do not, however, routinely place an intraarterial line in patients with an uncomplicated medical history.

Urine volumes and specific gravities must be followed along with sodium levels to assess the presence of diabetes insipidus. High doses of corticosteroids will frequently cause a subclinical state of DI to be manifest; we therefore taper corticosteroids as rapidly as possible postoperatively. In addition, one frequently encounters a secondary stage of water retention (?SIADH) following an initial bout of DI. Once this secondary stage, identified by a low serum sodium, is finished, the patient may transiently excrete a large volume of low specific gravity urine. This simply represents clearance of excess free water and should not be treated, since the majority of these patients will come into fluid balance on their own. It is imperative, however, to carefully follow the serum sodium in order to define this process.

Prior to discharge, an A.M. fasting serum cortisol is obtained to determine the need for cortisol replacement. Intraoperative evidence of residual normal pituitary gland is also a major guide in such considerations. Thyroid evaluation is usually done 3 to 4 weeks postoperatively, since autonomous function of the thyroid may persist for some time.

Unless clinically indicated, postoperative imaging is done no earlier than 6 weeks postoperatively, at 3 months in most cases. This allows resolution of all operative artifactual changes and assessment for residual tumor.

Management of the Poor-Risk Patient

In the elderly patient, or any patient with a medical illness that may increase the risk of complications from general anesthesia or surgery, consideration should be given to primary radiation therapy (RT) after clinical diagnosis of a nonfuctioning pituitary tumor. This nonsurgical approach is particularly appropriate in patients who already have hypopituitarism.

A dose of 4,000 cGy by external beam is considered optimal by most radiotherapists.[3,33] In a series of 12 patients treated with RT alone, Chun et al[8] described a 50% recurrence rate with a 75% local control following treatment. Other authors report a local control rate of 50-79%, with an adequate salvage in cases of recurrence.[23,36]

In the asymptomatic elderly patient with a nonsecreting tumor, intact pituitary function, and no compromise of the visual sys-

tem, a case can be made for merely monitoring the patient with routine visual and endocrine evaluation, and serial MRI or CT scanning at least yearly. These tumors may exhibit a benign course, without reaching symptomatic dimensions within the life expectancy of the patient.

Postoperative Radiotherapy

The rationale for postoperative RT is to reduce the incidence of recurrence. Several studies suggest improved tumor control with the combination of surgery plus radiotherapy.[6,8,9,28] This is especially true in large and invasive lesions, which manifest an increased rate of recurrence. RT by no means insures recurrence-free survival, but the time to recurrence may be prolonged.

Valtonen and Myllymaki[37] reported a surprisingly high 36% recurrence rate in patients with a "total removal" following transfrontal craniotomy and postoperative RT, with recurrences up to 18 years after therapy. Thus, published recurrence rates may be misleading in series with short follow-up times. This is an important consideration as morbidity and mortality both increase with reoperation in cases of recurrence.[25,37]

With functioning pituitary tumors, evaluation of postoperative endocrine status may give indication as to the effectiveness of surgical removal. However, in nonfunctioning lesions the judgment of the surgeon, supplemented by postoperative imaging, is the only means of assessing the extent of resection and the risk of recurrence.

The surgeon's appreciation of the totality of the resection may not be accurate in the face of an invasive tumor. The lack of a chemical marker in a true nonfunctional tumor makes assessment of cure difficult in the postoperative period. Furthermore, in contrast to prolactin and growth hormone-secreting tumors, no adjunctive pharmacotherapy is available.

For these reasons, the criteria for selection of patients for postoperative RT remain controversial. In general, patients with large tumors that have a high incidence of invasion of the dura and are difficult to surgically remove should all be considered candidates for postoperative RT, especially if the patient is hypopituitary postoperatively. Similarly, frank cavernous sinus invasion is an indication for postoperative radiation therapy. In those cases where tumor invasion is not evident, and "total" removal has been achieved, routine scanning on a yearly basis may be an appropriate strategy, especially if endocrine function is intact.

The Problem of Recurrence

The patient with a recurrent nonsecreting tumor may present a challenge, especially if the patient is young and has a normally functioning pituitary. In these cases, further treatment must be individualized, with options including repeat transsphenoidal surgery, salvage RT, or following the patient with serial imaging studies if he/she is functionally intact or stable. Prior radiation therapy may produce thinning of the bone at the skull base, and may predispose to postoperative leaks, but is never a contraindication to transsphenoidal surgery.[25] The situation is quite different following previous frontal craniotomy, which may produce scarring and distorted vascular anatomy, increasing the risk of reoperation.

Summary

The diagnosis of a nonsecreting pituitary adenoma relies on a constellation of radiographic, endocrinological, and clinical criteria. The management of the patient must be considered primarily surgical, with other therapeutic options individualized depending on symptomatology, endocrine status, age, and general health.

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