Treatment of Disorders of the Pituitary Gland: Pearls and Pitfalls From 30 Years of Experience

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It has been my privilege to care for a large number of patients with disorders of the pituitary gland over the past 30 years. I would like to share with you a few thoughts on the pearls and pitfalls that I have found in my experience.

I would emphasize that lesions involving the pituitary gland arise not only from within the gland, but also from the surrounding structures. A list of these lesions is long and includes a wide variety of tumors, with pituitary adenomas and craniopharyngiomas being the most common. *Table 3.1* lists the tumor types that are found in the parasellar region and also the wide range of infectious and inflammatory lesions, a number of different cystic lesions as well as vascular lesions that can appear in this area.

Although patients with pituitary lesions often present to endocrinologists or neurosurgeons, they more often are seen on the front lines by neurologists, ophthalmologists, otolaryngologists, and psychiatrists; in the emergency department; and, most importantly, by our colleagues in primary care and pediatrics. They are the ones who have to spot a patient with acromegaly or a patient with Cushing's disease in their waiting room.

Pituitary tumors are quite common. The most recent edition of the Central Brain Tumor Registry estimates that pituitary adenomas constitute 8.4% of brain and central nervous system tumors.[1]

They are the most common tumor in patients of ages 20 to 34 years and the second most common tumor in the 34- to 44-year age group. They are 30% more common in the black population.

We have found that forming a multidisciplinary pituitary clinic has been very helpful to our patients. Dr. Ariel Barkan, a pituitary endocrinologist, and I see all our patients together. We see them in the same room at the same time. We have other endocrinologists, neuroradiologists, neuro-oncologists, and neuro-ophthalmologists available for consultation when needed.

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I would now like to focus on some of the pitfalls that exist with these patients in hopes that you can learn from our experience.

First, a few observations about the workup of thyroid function. As you know, it is common in primary care to screen patients with suspected clinical hypothyroidism with just serum thyroid-stimulating hormone (TSH). Physicians need to remember that a pituitary lesion will result in *secondary* hypothyroidism. This is identified by a low free thyroxine (T_4), but a normal TSH. In *primary* hypothyroidism, the free T_4 is low, but the TSH will be markedly elevated.

A pitfall even when the free T_4 is available is seen in the following situation. A 28-year-old woman presented with a symmetrically enhancing mass in the sella (*Fig. 3.1A*) and low thyroid function, as evidenced by a low free T_4 of 0.56 ng/dL (normal, 0.7–1.8 ng/dL). What are the red flags in this picture? First, the mass is very symmetrical and uniformly enhancing, and, second, there is no TSH value. When we tested the TSH test, it was markedly increased to 126 mIU/L (normal, <7 mIU/L). This is consistent with primary hypothyroidism. The patient was treated with levothyroxine replacement, and the hypertrophy of the gland resolved (*Fig. 3.1B*).

The pearls here are the following:

1. Beware when a "tumor" has symmetrical enhancement. It may be a pseudotumor of primary hypothyroidism, as seen in the case described. Variants of hypophysitis, either lymphocytic or granulomatous, will also present on magnetic resonance imaging (MRI) as a symmetrically enhancing mass. Both of these conditions are treated medically; the thyroid pseudotumor (hyperplasia) is treated with thyroid replacement and hypophysitis is treated with prednisone.
2. Always order free T_4 and a TSH tests when the diagnosis of hypothyroidism is considered.

Another patient of ours illustrated yet another pitfall in thyroid testing. This 21-year-old woman presented with clinical signs of *hyperthyroidism* and was found to have an elevated free T_4 of 2.6 ng/dL (normal, 0.7–1.8 ng/dL) and a "normal" TSH of 3.0 mIU/L (normal, <7 mIU/L). At first glance, this would seem to be consistent with primary hyper-

TABLE 3.1. Sellar and parasellar lesions

Tumors	Infection/Inflammation	Cysts	Vascular
Adenoma	Bacterial abscess	Rathke's cyst	Aneurysm
Craniopharyngioma	Fungal abscess	Pituitary cyst	Carotid cavernous fistula
Meningioma	Sarcoidosis	Arachnoid cyst	Pituitary apoplexy
Chordoma	Tuberculosis	Empty sella	
Epidermoid	Hypophysitis	Sinus mucocele	
Dermoid	Histiocytosis X	Cystic adenoma	
Germinoma	Orbital pseudotumor	Cystic craniopharyngioma	
Neuroma			
Hemangioma			
Nasopharyngeal carcinoma			
Optic nerve glioma			
Choristoma			
Hypothalamic glioma			
Astrocytoma			
Lymphoma			
Angiolipoma			
Metastatic cancer			

thyroidism. The pearl here is that in primary hyperthyroidism, the TSH should be suppressed to an almost immeasurable level. Here the TSH is still in the middle of the normal range (3.0 mIU/L). MRI showed a 7-mm nodule that was calcified on computed tomography (CT) imaging. When the nodule was removed, the pathology revealed a TSH-secreting adenoma and her free T_4 returned to normal after surgery. Her symptoms related to hyperthyroidism resolved.

What about the pituitary-adrenal axis? To evaluate a patient for suspected hypocortisolism, it is critical to measure the serum cortisol at 8 AM. If the cortisol is extremely low (<5 μg/dL), the diagnosis can be confirmed. If the 8 AM cortisol level is greater than 16 μg/dL, you can be comfortable knowing that it is normal. If it is in the mid-range, it is often prudent to do an insulin hypoglycemia stress test to see whether the cortisol increases into the normal range.

Sorting out *elevated* corticotropin is much more complicated. As always, the workup begins in the primary care physician's office with a "clinical suspicion" of hypercortisolism.

The single best screening test is a pair of 24-hour urine collections for urinary free cortisol. Contrary to popular belief, the overnight dexamethasone suppression test is only accurate 80% of the time. If the diagnosis of hypercortisolism is confirmed and MRI of the pituitary gland is positive, the patient needs to go straight to surgery. If MRI findings are negative, as they are in 40% of patients with pituitary-dependent hypercortisolism, then bilateral inferior petrosal sinus sampling is needed. If the results are positive, pituitary exploration is indicated, and if negative, other causes need to be sought for the hypercortisolemia. The laterality identified during inferior petrosal sinus sampling is only 70% predictive of the side of the microadenoma.

The pearls in the workup of the pituitary-adrenal axis are the following:

1. The 8 AM serum cortisol is best to prove *hypocortisolemia.*
2. The 24-hour urinary free cortisol test is best to prove *hypercortisolemia.*
3. Inferior petrosal sinus sampling is best to prove pituitary origin, but laterality is only accurate 70% of the time.
4. Forty percent of Cushing's patients have normal imaging.

Let me make a few comments on the surgical approach that I use for resection of a microadenoma.

I switched many years ago from the sublabial to the transnasal approach. This approach is much easier for the patient and allows excellent visualization of the sella. I do all these approaches myself, but it is perfectly acceptable to use an ENT surgeon to assist with the approach.

For the transnasal approach, I use a standard Killian speculum with a side-locking screw. The operating microscope is used from the outset of the case. The first thing that you see when you enter the nose is the inferior turbinate. As the speculum is advanced, you see the middle turbinate. It is important to be certain that you are medial to the middle turbinate, next to the midline septum of the nose. The direc-

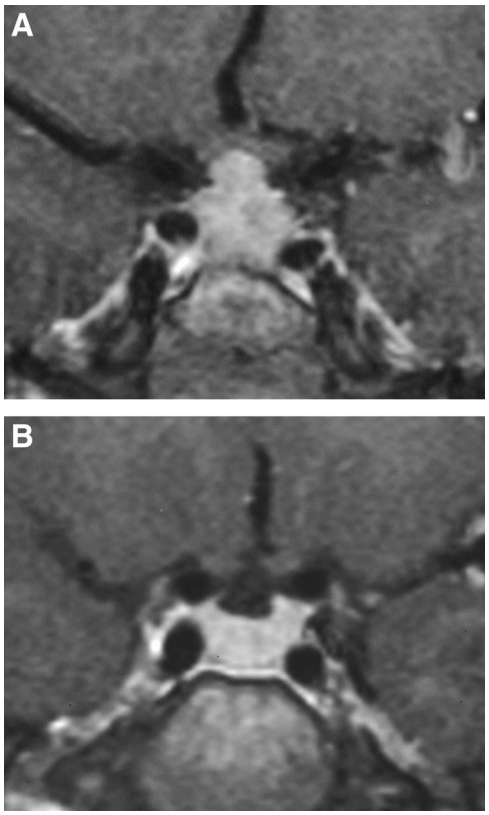

FIGURE 3.1. *A,* Contrast-enhanced T1-weighted coronal magnetic resonance image of a pituitary gland showing a symmetrically enlarged gland with elevation of the optic chiasm. *B,* Contrast-enhanced T1-weighted coronal magnetic resonance image of the pituitary gland showing shrinkage of the hyperplastic gland after treatment of primary hypothyroidism.

tion of the speculum is in line with the middle turbinate, but the direction is checked periodically with lateral fluoroscopy.

When you reach the anterior wall of the sphenoid sinus, you coagulate the overlying mucosa and gently punch through to the sinus. A critical instrument in this approach is the extension on the Bovie device that allows it to reach at least 10 cm into the nose. I bend the Bovie extension at approximately 45 degrees to allow easy visualization. Various size Kerrison punches are used to remove the anterior wall of the sphenoid sinus, first on the side of the approach and then across the midline to the opposite side. I find that this is most easily accomplished by undercutting the midline bone with a right-angle 3-mm Kerrison punch. Once you have undercut the midline to the opposite side, you can easily push the nasal septum in that direction and gain a direct view of the sella.

In patients with a normal sella, such as in a Cushing's microadenoma, it is useful to open the sella with a high-speed drill. It is important to have a drill system that is at least 100 mm in length so that it will reach the sella. A 1-mm Kerrison punch is used to further remove bone, and then the dura is opened transversely and inferiorly. It is best to stay away from the upper third of the dura, as you will often see cerebrospinal fluid (CSF) leakage from arachnoid recesses in this area. The gland is then dissected; look first on the side of the magnetic resonance–imaged tumor or, if the MRI is normal, on the side of the positive petrosal sinus sampling. It may be necessary to open the gland itself with a small scalpel blade. If a tumor is not identified on the side of the positive petrosal sinus sampling, then it is imperative to explore the opposite side. It is ideal to find the plane between the tumor and gland and to remove the tumor en bloc.

For closure, I reconstruct the anterior wall of the sella with a bone graft if CSF has been seen. I use either bone that has been saved from a sphenoid sinus septum or allograft iliac crest bone. If there has not been any CSF leakage, then I just cover the opening to the sella with tissue glue and fill the sphenoid sinus with fat harvested from the abdomen. A small Telfa pack is placed over the opening to the sphenoid sinus, and the speculum is removed. Any bleeding from the nasal mucosa is stopped with bipolar coagulation. Patients can breath easily even with the pack in place. The pack is removed before discharge the next morning.

Frameless navigation can be extremely helpful in selected situations. How often it is used depends on the experience of the surgeon and the size and configuration of the tumor. I use it routinely for very small tumors with normal sellar anatomy, but not for very large tumors with sellar floor enlargement or erosion. I also find it helpful in patients who have had previous sellar surgery. I would find it perfectly acceptable for a surgeon to use it in every transsphenoidal approach if the surgeon's experience is limited. It provides three-dimensional imaging and adds safety to the procedure. I always use it in combination with lateral fluoroscopy, so that you have real-time imaging in two planes to check the accuracy of the frameless navigation system.

I first started using frameless navigation when I was operating on a patient with Cushing's disease and a normal pituitary gland on imaging. At the time of surgery, he was found to have numerous and very complex septa within his sphenoid sinus. I had started to drill what I thought was the midline anterior wall of the sella, but became uncomfortable with the anatomy, so I stopped, backed out, and did a Stealth CT scan.

This showed that I was off the midline to the left and had drilled bone directly over the carotid artery. I took the patient back to the operating room and, using the CT images in a frameless navigation system, easily found my way to the sella. A microadenoma was found, and he experienced an excellent remission from his hypercortisolism.

Frameless navigation can be accomplished for pituitary surgery by obtaining either preoperative or intraoperative imaging. I have found that 3-dimensional CT imaging is more helpful that MRI because it is the fine bone anatomy that is

most important. We developed a system that allows us to acquire 3-dimensional images of the bony skull base and simultaneously register it into the Stealth frameless stereotactic system (Medtronic Sofamor Danek, Memphis, TN).[3] We use the Arcadis Orbic (Siemens Medical Solutions, Malvern, PA) system to acquire the 100 x-rays used to generate the 3-dimensional images and also for lateral fluoroscopy during the case. The final images are virtually identical to CT images that would be acquired from a separate preoperative study. This system allows accurate imaging and registration in one step and eliminates the need for a preoperative study. This system was developed for spine use, but works perfectly for the skull base.

The pearls are as follows:

1. Stop and back out when you are uncertain.
2. Use frameless navigation liberally.

How do we assess remission after microsurgical resection of a corticotropin-secreting adenoma? Ideally, the postoperative cortisol levels drop into the subnormal range, usually below 3 μg/dL. If they are decreased from elevated preoperative levels to just normal, the recurrence rate is higher. Generally when the cortisol level is normalized, patients will show a remarkable resolution of their Cushing's signs and symptoms. Clinical recovery is usually "all or none." Decreasing the cortisol levels short of normal does not result in clinical improvement.

With resection of a corticotropin-secreting microadenoma seen on MRI, we achieve a biochemical remission in more than 90% of patients. If the imaging is negative, the remission rate decreases to approximately 75%, and in macroadenomas, the biochemical remission rate is just 66%.

Although surgery is clearly the initial treatment for Cushing's disease, there are still approximately 10% of patients in whom surgery fails and as many as 25% who will experience a recurrence.[5]

When performing surgery for Cushing's disease, you should be willing to take the patient back for repeat surgery. If the petrosal sinus sampling is convincingly positive for a pituitary origin of hypercortisolism and partial resection fails to provide a remission, you should go back and remove the rest of the gland. On one occasion, I did this, and the second specimen contained a 1-mm corticotropin-secreting adenoma and the patient was in remission. On another occasion, the pathology on the initial specimen from a partial resection showed diffuse corticotropin hyperplasia. I went back and removed the rest of the gland and the patient was in remission. The diagnosis of hyperplasia requires resection of the entire gland to provide remission.

In patients in whom surgery fails, a combination of medical therapy and radiation generally will control the disease.

The pearls are:

1. Success in Cushing's disease is all or none. The patient does not just "get a little bit better."
2. Be willing to go back for another look.

In acromegaly, once again, clinical suspicion is the key entry point to this disease. Once suspected, the workup of acromegaly is easy as long as your remember to order an insulin-like growth factor 1 (IGF-1) test (Somatomedin C). IGF-1 is always elevated, but not infrequently the growth hormone (GH) will be completely normal. Occasionally, we will see a patient with increased IGF-1 and GH, but an essentially normal physical examination. Remember that acromegaly has a significant negative impact on survival, and this becomes worse if the patient has diabetes and/or heart disease.

We recently had a patient who was clinically clearly acromegalic and had a pituitary tumor, but the GH was normal and the IGF-1 was only minimally elevated. We discovered that she was taking estrogen, and when this was stopped, her IGF-1 increased to 1345 ng/mL.

Overall, approximately 55% to 60% of those with acromegaly will be in remission after surgery alone. Remission after surgery for microadenomas is approximately 80% and just 45% for macroadenomas. Unfortunately, unlike in Cushing's disease, macroadenomas are more common in acromegaly. Fortunately, any amount of lowering of GH will result in improvement of preoperative symptoms. Clinical success is related more linearly than the "all-or-none" situation in Cushing's disease.

Another important observation is that often IGF-1 decreases only gradually after surgery, sometimes taking several weeks or months to reach its lowest level.

When surgery fails, there are now very good medications that can be used. The somatostatin analogues are the most effective. These include octreotide (Sandostatin LAR) and lanreotide (Somatuline Depot). These medications are effective approximately 65% of the time in normalizing IGF-1. If these fail, the GH receptor blocker pegvisomant (Somavert) can be used. Because pegvisomant works at the peripheral receptor level, it is possible that the primary pituitary would continue to grow with this treatment. The dopamine agonist cabergoline will occasionally help to lower GH and IGF-1 but works more often in the mammosomatotrophic tumors that produce both GH and prolactin.

Radiation still plays a role in treating surgical failures, although we only use it when surgery and medical treatment fail. With postoperative radiation, it is best to start with as low as possible GH level, because GH decreases only 50% in the 2 years after radiation, and it takes 7 years to decrease by 80%. Single-dose radiosurgery is equal in effectiveness to fractionated radiation and may be more convenient for some patients.

The pearls for acromegaly are:

1. GH may be normal.
2. Estrogen will suppress IGF-1.
3. Reduction in tumor mass is clinically helpful (not "all or none").
4. It may take weeks to months for IGF-1 to decrease postoperatively.
5. Most postoperative failures can be controlled medically: first, somatostatin analogues (octreotide, lanreotide) and then pegvisomant.
6. Radiation is a last resort, either fractionated or radiosurgery.
7. Reoperation is rarely useful.

Most prolactin-secreting pituitary adenomas are treated medically. The most common medication today is the dopamine agonist cabergoline. This is effective in both microadenomas and very large macroadenomas. It can even be effective clinically and biochemically in hemorrhagic prolactinomas. Occasionally, prolactinomas are unresponsive to cabergoline or the patient cannot tolerate the medication, and surgery is therefore indicated.

It is critical to measure prolactin in all patients with pituitary tumors. Usually a significant increase in prolactin is obvious, but occasionally it is hidden by the "hook effect." The hook effect occurs when the prolactin is extremely high (usually more than 10[thinsp]000 ng/mL), but the reported result may be only a minor increase (e.g., 40 ng/mL).

Currently, prolactin is measured by immunoradiometric or immunoluminometric assays, both using 2-site technology. These assays offer rapid and accurate measurement, but have the pitfall of the so-called hook effect. Thus, in any patient having a large pituitary mass (usually >4 cm), prolactin needs to be measured in a 1:1000 diluted sample. Failure to do so may lead to an erroneous diagnosis of a nonfunctioning adenoma and inappropriate surgery instead of medical treatment with a dopamine agonist.

Pearls for prolactinomas are as follows:

1. Measure prolactin in all patients with a pituitary tumor.
2. Perform serial dilutions (up to 1:1000) in all patients with large tumors.
3. Most prolactinomas can be treated with a dopamine agonist.

The so-called extended transsphenoidal approach is used to reach tumors in the parasellar area. Tumors of the clivus, inferior to the sella, can readily be approached transsphenoidally. Tumors of the pituitary stalk, such as small craniopharyngiomas, can be reached by extending the exposure superior to the sella, through the diaphragma sellae, and often with removal of part of the tuberculum sellae. Some surgeons prefer to remove selected meningiomas of the tuberculum sellae region transsphenoidally by removing the bone at the base of the tumor. This avoids a craniotomy, but increases the risk of CSF leak postoperatively. Recent series report 20% to 40% rates of CSF leak with the extended transsphenoidal approach for craniopharyngiomas and meningiomas[2,4] compared with less than 1% with pituitary adenoma surgery.

I do not use the endoscope routinely, but have it available when needed. I prefer the 3-dimensional microscope, but a few pituitary surgeons prefer to do most of their transsphenoidal surgery exclusively with the endoscope. It has the unique advantage of viewing at a 30- or 45-degree angle at its tip, but generally requires a larger exposure and often a full-time assistant surgeon to manage the endoscope. The great disadvantage is that the image produced is only 2-dimensional.

We need to keep in mind that open intracranial surgery continues to be valuable in the treatment of parasellar tumors. I use the subfrontal approach for all parasellar meningiomas and the majority of craniopharyngiomas. So far, the operating time and CSF leak rates are less than those reported for the extended transsphenoidal approach for meningiomas. I occasionally see tumors of the optic pathways, including gliomas, and even one case of Langerhans granuloma of the optic chiasm. These are best approached intracranially.

Disclosure

The author has no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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