

PITUITARY TUMORS: A PRIMER


Edward Vates, MD, PhD


Assistant Professor, Department of Neurosurgery
Co-Director, Multidisciplinary Neuro-Endocrine Clinic
University of Rochester Medical Center

Laura Calvi, MD

Associate Professor, Division of Endocrinology
Co-Director, Multidisciplinary Neuro-Endocrine Clinic
University of Rochester Medical Center

This handout is for informational purposes only, and should not be construed as definitive treatment recommendations. Medical knowledge is constantly evolving, and this information cannot substitute for current state-of-the-art medical therapy.

 **Basic Pearl #1** a complete endocrine panel helps with initial diagnosis & management. It should include the following serum tests: LH, FSH, TSH, free T4, prolactin, ACTH, GH, IGF-I (aka somatomedin-C), estradiol (women & men), testosterone free and total (men), and cortisol. If you can get this test drawn in the morning that is ideal, but it does not need to be fasting. This panel of tests will cover the bases and direct more tailored testing as needed.


 **Basic Pearl #2** if you are going to get an MRI, it is essential that it be AT LEAST a 1.5 Tesla closed MRI, and you should ask for a pituitary MRI with dynamic contrast study. A 3 Tesla MRI is available UPMC, and provides increased resolution of small pituitary tumors. If your patient can't have contrast (renal dysfunction, prior history of allergic reaction to gadolinium), go ahead and get a pituitary MRI without contrast. If your patient can't have an MRI, then consider a CT angiogram or CT sinuses with contrast.

Classification

There are many different kinds of tumors that can arise in the pituitary/sellar region (see right). We will focus on PITUITARY ADENOMAS because they are the most common, with a population prevalence of 10-20% based on autopsy & MRI series. In spite of being common, they are often asymptomatic (see *Dilemma: the pituitary "incidentaloma"* below).

Pituitary adenomas can be thought of in two broad categories: endocrine-active adenomas & endocrine-inactive adenomas (aka "null cell" or non-functioning, although this is a misnomer). Endocrine-active tumors are much more common (2:1), and can be further subclassified based on the hormone secreted by the tumor: ACTH (Cushing's disease), GH (acromegaly), prolactin, or TSH (*extremely rare*). FSH/LH secreting tumors most likely end up in the endocrine-inactive tumor division because when these hormones are hypersecreted they are non-functional (thus "null cell" is a misnomer).

Pituitary/Sellar Tumors:

90%  Pituitary adenoma
Rathke cleft cyst
Pars intermedia cyst
Craniopharyngioma
Epidermoid tumor
Colloid cyst
Chordoma
Meningioma
Metastatic carcinoma
Inflammatory/infiltrative disorders

Common presenting symptoms and work-up


Endocrine-inactive adenomas present with symptoms related to mass effect: hypopituitarism, cranial nerve compression, headache


Headache is a very common feature of pituitary tumors, but headache is also common for lots of other reasons, so head pain relief is not a compelling reason to treat a pituitary tumor...in other words, surgery might make the patient's headache better but can give them another reason to have a headache.

Hypopituitarism only sets in when the tumor is a macroadenoma (microadenoma < 1cm, macroadenoma > 1cm).

Increasing pressure on the normal pituitary gland causes hormone dysfunction in the following order: depressed GH/IGF-I → depressed LH/FSH (hypogonadotropic hypogonadism) → elevated prolactin (hyperprolactinemia) → depressed TSH (central hypothyroidism) → depressed ACTH (hypocortisolemia leading to Addison's disease)

Cranial nerve compression typically presents with compression of the optic chiasm that sits right over the sella (bitemporal hemianopsia), but if there is compression or invasion of the cavernous sinuses you can also have diplopia (CN III, IV or VI) or facial numbness (trigeminal), although this is rare.

 Symptoms & signs of hyperprolactinemia depend on sex, and in women the effects depend on hormonal status (see below), but in all pre-menopausal women it is critical to exclude pregnancy.

 Hyperprolactinemia due to compression (aka *stalk effect*) almost never exceeds 200...anything over that is an endocrine-active prolactinoma. Conversely, anything < 150 may respond to bromocriptine/cabergoline, but it is not actually treating the tumor, merely suppressing the effect of stalk compression.

Endocrine-active adenomas present with symptoms related to the hypersecretion syndrome, and rarely from mass effect (prolactinomas in men are the exception to this rule)

QUESTIONS OR REFERRALS: (585) 273-2343

EMAIL: edward_vates@urmc.rochester.edu or laura_calvi@urmc.rochester.edu

ACTH-Cushing's disease

Central adiposity, diabetes, hypertension, hirsutism, acne, depression/anxiety, connective tissue fragility, striae, easy bruising, osteopenia/porosis, hypercalcuria, steroid myopathy



1/3 of GH-secreting adenomas co-secrete prolactin, so JUST CHECKING A PROLACTIN LEVEL ISN'T ENOUGH (see Basic Pearl #1)

GH-Acromegaly/Gigantism

Soft tissue swelling, prognathism, frontal bossing, deep voice, sleep apnea, joint pain, excessive sweating, diabetes or impaired glucose tolerance, carpal tunnel, cardiomegaly, hypertension

Prolactin

Pre-menopausal women: amenorrhea, galactorrhea, decreased libido
Post-menopausal women: breast tenderness, decreased libido, decreased bone mineral density
Men: decreased libido, impotence

Diagnostic confirmation obviously depends on the hypersecreted hormone:

- 1) confirm hypercortisolemia: check 24-h urine free cortisol OR midnight salivary cortisol (a new test) AND ACTH
- 2) confirm ACTH-dependent hypercortisolemia: measure a.m. ACTH & cortisol simultaneously
- 3) confirm pituitary source: check high dose dexamethasone suppression test & IPSS (see below)
- 4) check MRI

- 1) check IGF-I (GH is pulsatile but IGF-I summates the effects)
- 2) confirm GH abnormality: check oral glucose tolerance test
- 3) check MRI



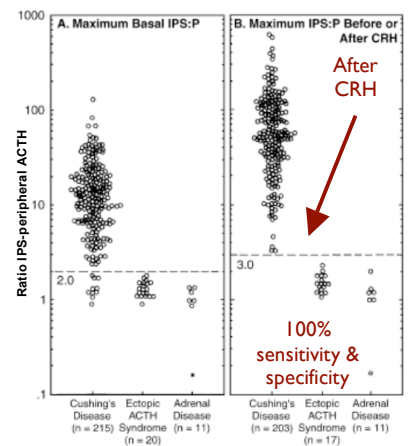
**1.5 – 3 Tesla closed MRI
pituitary protocol with
dynamic contrast study**

- 1) confirm hyperprolactinemia: check serum prl (>200 ng/dl) make sure to do dilutions make sure to check for GH & IGF-I
- 2) make sure patient isn't pregnant: check β -HCG if premenopausal
- 3) rule out hypothyroidism: check TSH & free T4
- 4) if prl between 50-200, make sure there are no other medical factors
- 5) check MRI



Hyperprolactinemia can be due to a number of causes. In pre-menopausal women it is critical to ALWAYS RULE OUT PREGNANCY. Hypothyroidism is otherwise the most common cause of hyperprolactinemia, and should always be considered, but there are many other medications that can cause elevation of prolactin, including many psychiatric medications (phenothiazines, MAOI's, fluoxetine, butyrophenones, tricyclics, and amoxipine), antihypertensives (methyldopa, Ca^{+2} -channel blockers and reserpine), estrogens, metoclopramide, H_2 -receptor blockers (cimetidine, ranitidine), and opiates. Other causes of non-physiologic hyperprolactinemia that need to be considered include renal failure, liver failure, breast stimulation, other conditions that can mimic breast stimulation (e.g., chest wall or spinal cord lesions), stress and seizures.

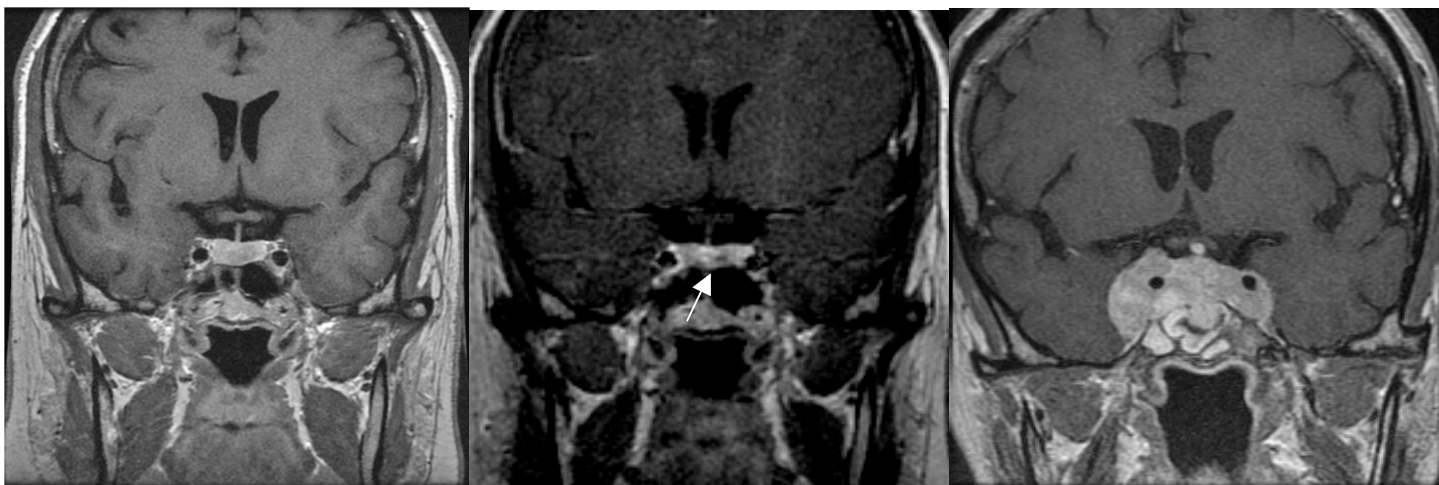
What is inferior petrosal sinus sampling (IPSS)? This is a way of differentiating between a pituitary source for hypercortisolemia (i.e., Cushing's disease) and either an ectopic ACTH source (lung tumor) or an adrenal tumor secreting cortisol. An interventional radiologist manipulates catheters into the inferior petrosal sinuses *bilaterally*, samples the venous drainage from the pituitary gland, and compares the inferior petrosal ACTH level to the peripheral ACTH level before and after injection of corticotrophin releasing hormone (CRH, the hypothalamic stimulant for ACTH release from the pituitary). Before CRH injection, 95% of patients with a pituitary adenoma causing Cushing's will have an IPSS/peripheral ACTH ratio ≥ 2 (because the tumor secretes ACTH that feeds into the IPSS). However, the sensitivity and specificity of the test increases to 100%/100% by injecting CRH and measuring the IPSS/peripheral ratio again; an ACTH-secreting pituitary adenoma will still respond to CRH, and an IPSS/peripheral ratio ≥ 3 is incontrovertible evidence of Cushing's disease. (figure from Oldfield EH, Doppman JL, Nieman LK, et al. N Engl J Med 1991;325(13):897-905). Note however that IPSS cannot always be performed successfully because of variations in individual anatomy of the venous sinuses.



Imaging

MRI has become standard for the evaluation of pituitary tumors, and in most cases no treatment recommendations would be made without a high quality study that allows for accurate and precise description of the anatomy. Most MRI facilities in Rochester are able to perform MRI with pituitary protocol (a "coned in" view of the sella) with post-contrast coronal and sagittal images, and can also provide dynamic contrast imaging.

What is a dynamic contrast MRI? Almost all pituitary tumors enhance, but so does the normal pituitary gland...in fact it enhances even more brightly. However, compared to the normal pituitary gland (which enhances quickly), most pituitary adenomas enhance more slowly because of the disorganized microvasculature. You can take advantage of this using a dynamic contrast study; even small pituitary tumors (as small as 1-2 mm) will show up when the MRI images are acquired while the contrast is being injected because the normal pituitary gland will start to enhance before the tumor, thereby showing the tumor more accurately as a dark "shadow" within the brightly-enhancing, normal pituitary gland



A small Cushing's tumor is invisible on the regular post-contrast MRI scan.

The small tumor is only visible on the dynamic contrast study.

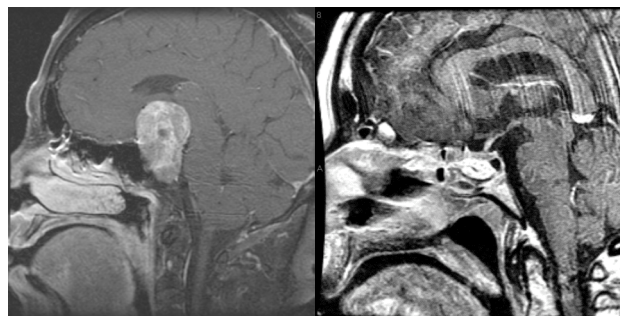
Not all tumors require a dynamic contrast study to be seen; this patient's prolactin level was >9000.

Management decisions: medical, surgical and radiation options

Goals of therapy depend on many factors: endocrinopathy (hypersecretion/hypopituitarism), symptoms from compression, tumor size and relationship to normal anatomy, patient age and medical comorbidities. Fortunately, for the vast majority of patients, we are able to offer a combination of medical, surgical, and radiation therapies that can control their symptoms, prevent tumor progression, and in many cases patients can even be cured, but this requires close collaboration between care givers from many different disciplines. In addition, even a "cured" patient cannot be released from routine follow-up because remote recurrences can occur, and for endocrine active tumors this can be especially devastating.

When is surgery appropriate? Any patient with either Cushing's disease or acromegaly has a potentially life-threatening endocrinopathy. Surgery offers a chance for cure when the tumor is small and the surgeon is experienced. Cushing's tumors can be especially small (many are symptomatic at 1-2 mm size) so finding the tumor is critical and experience is important. Even when a cure is achieved, there is a 25-30% recurrence rate because Cushing's tumors can be highly invasive microscopically. Recurrences can frequently be controlled with either further surgery or with radiotherapy. Acromegalic tumors often present insidiously, and as a result many are too large to achieve a cure with surgery, but debulking of the tumor reduces the level of endocrinopathy and also allows for scaled-down radiation treatment, thereby sparing normal tissues from radiation exposure and also reducing the likelihood of post-radiation hypopituitarism.

Endocrine-inactive tumors > 1 cm in size (macroadenomas) should be seriously considered for surgery except in the medically infirm or elderly. Macroadenomas typically cause pituitary compression and eventually hypopituitarism, but if the patient is asymptomatic then they can continue to be watched. The patient needs to be counseled on the risks of pituitary apoplexy (see below) and the unknown effects of asymptomatic hypopituitarism. Endocrine-inactive macroadenomas with symptomatic endocrinopathy or other demonstrable symptoms (e.g., bitemporal hemianopsia) should be removed surgically, and obviously very large tumors should be seriously considered for resection even if asymptomatic.



A pituitary macroadenoma in a post-menopausal woman with headaches, decreased libido and bitemporal hemianopsia.

Post-op MRI shows complete resection of the tumor with preservation of the normal pituitary sitting over residual fat graft.

Endocrine-inactive tumors < 1 cm (microadenomas) are unlikely to be causing hypopituitarism due to compression, and certainly are not big enough to cause other problems due to mass effect; these tumors may remain stable in size and can be followed radiographically and considered for resection if they show growth.

Medical therapies for pituitary adenomas: Medication is first line Rx for prolactinomas, not so for ACTH and GH secreting tumors.

PROLACTINOMAS: Even very large prolactinomas with visual compromise should be treated first with medication. Dopamine agonists are highly effective in normalizing prolactin levels (80-90%) and 69% of tumors show a >25% reduction in size (40% have >50% reduction in size). Bromocriptine and cabergoline are both available in generic forms, and the latter is preferable because of less side effects (nausea, vomiting and orthostatic hypotension being the most frequent with either Rx), duration of action (twice weekly vs. daily dosing), and it is more effective at reducing the size of tumors. Bromocriptine is preferred, however, in women who want to become pregnant, even though the safety data with cabergoline is starting to accumulate as more women get pregnant while on medication. In rare cases, surgery may be indicated if the patient cannot tolerate medical Rx or is young and doesn't want to take meds lifelong.

ACROMEGALY: Octreotide (Sandostatin) is a somatostatin analogue that is administered intramuscularly, and it reduces GH/IGF-I in 80-90% of patients, although it normalizes these values in only 40-50% of patients. It also has a short half-life, requiring multiple injections daily; a long-acting form is now available, requires dosing q4-6 weeks, and appears to be more effective, but can be associated with diarrhea and abdominal pain. Pegvisomant (a GH receptor inhibitor) is also available, but is not as well studied.

CUSHING'S DISEASE: Drug Rx for Cushing's disease is suboptimal; treatment should be directed at tumor removal and, if this is unsuccessful, return to a eucortisolemic state through bilateral adrenalectomy with hydrocortisone replacement Rx. Pharmacologic management is rarely possible, using agents directed at decreasing adrenal steroid secretion (ketoconazole, metyrapone, mitotane). All of these drugs have significant side effects, and frequently become ineffective over time because the decrease in cortisol results in enhanced ACTH secretion from the residual/recurrent tumor, leading to escape from the competitive block of steroid biosynthesis.

Radiation therapies for pituitary adenomas: Radiotherapy remains an important adjunct for treating patients with endocrine-active and endocrine-inactive pituitary adenomas that persist after surgery, are inoperable, or are resistant to medical therapy. Radiotherapy can be either stereotactic radiosurgery (SRS) or fractionated radiation therapy (FRT). Control of tumor growth is >95% with either therapy, but recent studies suggest that endocrine-active adenomas respond more quickly to SRS than to FRT (chemical remission at a mean of 2 years with SRS, 5 years with FRT). The durability of remission remains uncertain because most SRS studies do not have >5-10 year follow-up. In addition, this may be confounded by the fact that SRS is used for smaller tumors that may respond faster (SRS is reserved for smaller tumors because of the higher doses of radiation used at a single fraction). Interestingly, ACTH-secreting tumors appear to be the most radiosensitive, with one study showing a 100% response rate. It remains uncertain whether hormone-suppressing medication during radiotherapy decreases the response to radiation, and for SRS the safety profile remains unproven because most studies show onset of hypopituitarism at a median time of 84 months, whereas the mean follow-up time in most studies is only 36-48 months. Visual toxicity appears to be low, with most studies showing very few patients with complaints of new vision problems, although the sensitivity of patient complaints may be lower than formal visual field testing; this also most likely represents some selection bias, with SRS reserved for patients who do not have tumor near the optic chiasm. We are currently using fractionated stereotactic radiotherapy (SRT) for patients who are not candidates for SRS; this merges the use of standard linear accelerators with highly conformal delivery systems to provide therapy to small volumes that minimize the risk of hypopituitarism, and we are currently engaged in a study to compare SRT to SRS and FRT.

Pituitary Apoplexy

This is the most dreaded consequence in patients harboring a pituitary adenoma, but fortunately it is very rare, constituting 1-2% of patient presentations in most large series. The syndrome is defined as: sudden onset headache, nausea, vomiting, visual disturbances, oculomotor paresis, progressing to drowsiness, altered mental status and sometimes coma in a 24-48 hr timeframe. It usually arises because of sudden change in tumor size due to tumor infarction or intra-tumoral hemorrhage. This is a clinical not a radiographic diagnosis (i.e., an MRI showing hemorrhage in a pituitary tumor does not equate with pituitary apoplexy). The treatment is immediate steroid replacement (hydrocortisone 100 mg iv) and transsphenoidal exploration to decompress the pituitary region and to provide diagnosis in patients without a history of pituitary adenoma (other possible causes of pituitary apoplexy include abscess, metastatic tumor, lymphocytic hypophysitis, or hemorrhage associated with pregnancy). With timely intervention, this is rarely a fatal condition and most patients have return of visual function, but hypopituitarism usually persists.

Dilemma: the pituitary "incidentaloma"

Autopsy series suggest a prevalence of 10-12% for pituitary tumors (micro- and macroadenomas), and immunohistochemical evidence suggests 40-50% are prolactin (+). With increasing use of CT and MRI, more pituitary "incidentalomas" are being discovered, raising concern about what to recommend to patients harboring asymptomatic lesions; patient and physician anxiety must be balanced by what we know about pituitary tumors and the costs of unnecessary tests. Negative tests provide reassurance and improve quality of life, but extensive testing is expensive and may result in further expense and harm as false positive tests are pursued, creating a chain of events that proceeds with increasing momentum until it is difficult to stop. In general, we recommend the following for an incidentally discovered microadenoma: a one-time full endocrine screening panel, and a follow-up MRI in one year. If the endocrine tests are normal and the follow-up MRI shows no tumor growth, then a yearly prolactin level and IGF-I test are sufficiently sensitive to detect the most likely "bad" developments: increasing tumor size to a macroadenoma (which would cause IGF-I to fall and prolactin to rise) or conversion to an endocrine-active tumor (prolactinomas being the most likely). If symptoms indicate transition into an ACTH-secreting or TSH-secreting tumor, then further testing is needed.

References

- Daly, AF, Burlacu, MC, Livadariu, E, Beckers, A. The epidemiology and management of pituitary incidentalomas. *Horm. Res.* 2007, 68(suppl 5): 195-198.
- Dubuisson, AS, Beckers, A, and Stevenaert, A. Classical pituitary tumour apoplexy: clinical features, management and outcomes in a series of 24 patients. *Clinical Neurol. & Neurosurg.* 2007, 109: 63-70.
- Greeman, Y, and Melmed, S. Diagnosis and management of nonfunctioning pituitary tumors. *Annu. Rev. Med.* 1996, 47: 95-106.
- Findling, JW, Raff, H. Cushing's syndrome: important issues in diagnosis and management. *J Clin. Endocrin. & Metabol.* 2006, 91(10): 3746-3752.
- Freda, PU, and Wardlaw, SL. Diagnosis and treatment of pituitary tumors. *J Clin. Endocrin. & Metabol.* 1999, 84 (11): 3859-3866.
- Hammer, GD, Tyrrell, JB, Lamborn, KR, Applebury, CB, Hannegan, ET, Bell, S, Lu, A, and Wilson, CB. Transsphenoidal microsurgery for Cushing's disease: initial outcome and long-term results. *J. Clin. Endocrin. & Metabol.* 2004, 89(12): 6348-6357.
- King, JT, Justice, AC, and Aron, DC. Management of incidental pituitary microadenomas: a cost-effectiveness analysis. *J Clin. Endocrin. & Metabol.* 1997, 82(11): 3625-3632.
- Kong, DS, Lee, JJ, Jim, DH, Kim, KW, Nam, DH, Park, K, and Kim, JH. The efficacy of fractionated radiotherapy and stereotactic radiosurgery for pituitary adenomas. *Cancer* 2007, 110(4): 854-860.
- Lindsay, JR, and Nieman, LK. Differential diagnosis and imaging in Cushing's syndrome. *Endocrinol. Metab. Clin. N. Am.* 2005, 34: 403-421.
- Minniti, G. Fractionated stereotactic conformal radiotherapy for secreting and nonsecreting pituitary adenomas. *Clinical Endocrinol.* 2006, 64: 542-548.
- Minniti, G, Esposito, V, Piccirilli, M, Fratticci, A, Santoro, A, Jaffrain-Rea, M-L. Diagnosis and management of pituitary tumours in the elderly. *European J. Endocrin.* 2005, 153: 723-735.
- Mitsumori, M. Initial clinical results of linac-based stereotactic radiosurgery and stereotactic radiotherapy for pituitary adenomas. *Int. J. Radiat. Oncol. Biol. Phys.* 1998, 42: 573-580.
- Pickett, CA. Diagnosis and management of pituitary tumors: recent advances. *Prim. Care Clin. Office Pract.* 2003, 30: 765-789.

