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Pituitary Adenomas/PITNETS

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Objectives

1. Definition of Pituitary adenomas/tumors, prevalence, clinical presentation, diagnosis, DDX's and treatment
2. Hyperfunctioning Pituitary Adenomas- Etiology , clinical presentation, diagnosis, DDX and treatment
3. Hypopituitarism- Etiology, clinical presentation, diagnosis, DDX's and treatment

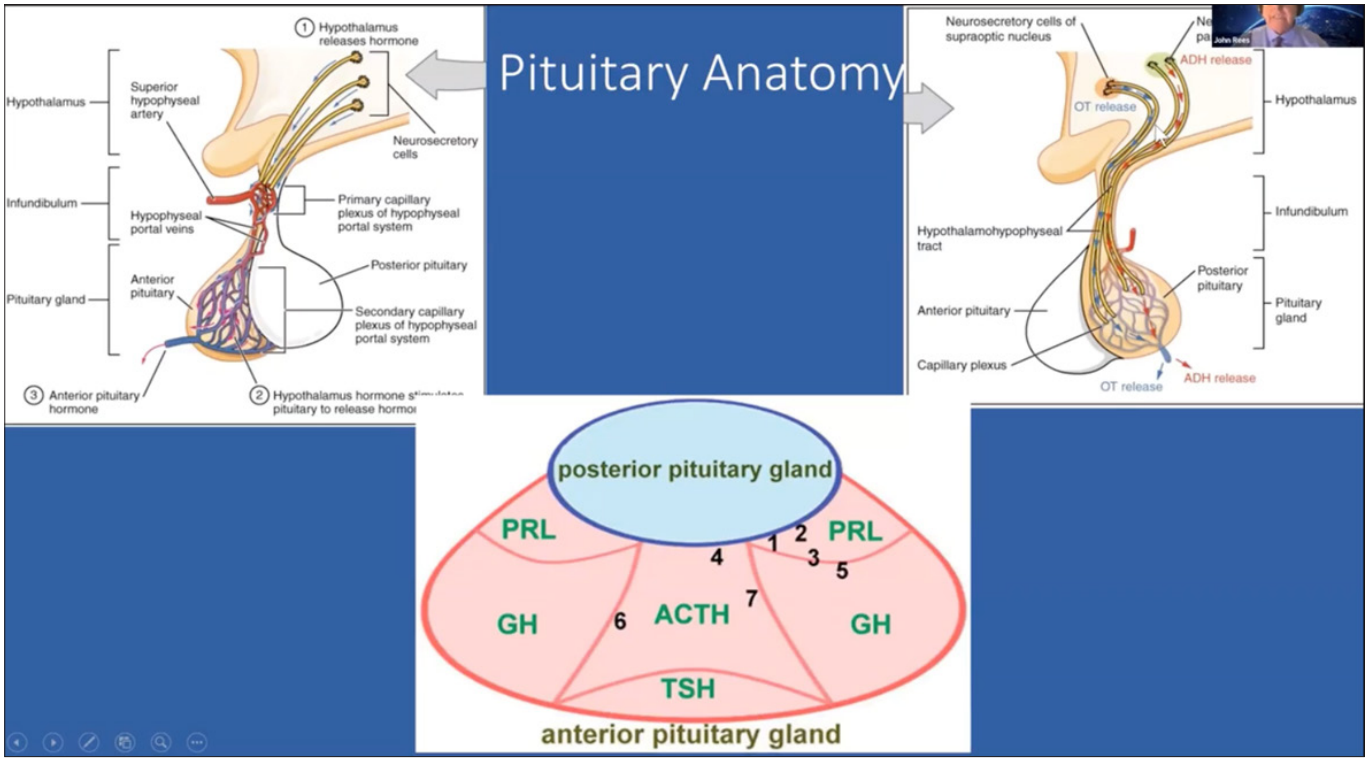
Pituitary Gland

Anterior Pituitary

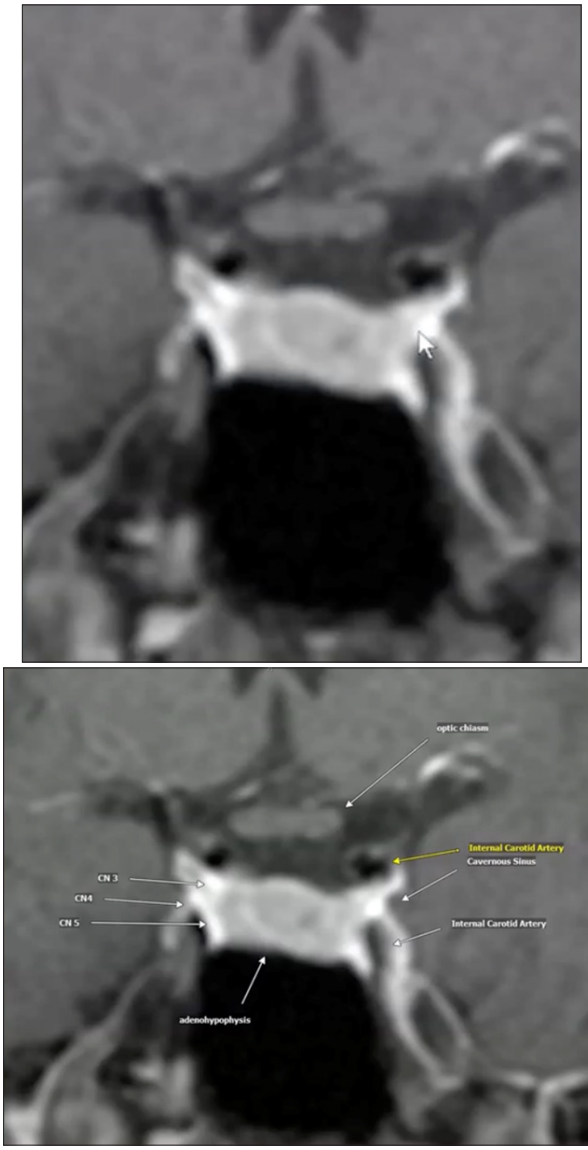
- Adenohypophysis
- 80% of the gland
- Derived from Rathke's pouch
- (oral ectoderm)
- Comprised of 5 cell types
- Secretes 6 hormones
- Controlled by neuropeptides from the hypothalamus & feedback from target organs

Posterior Pituitary

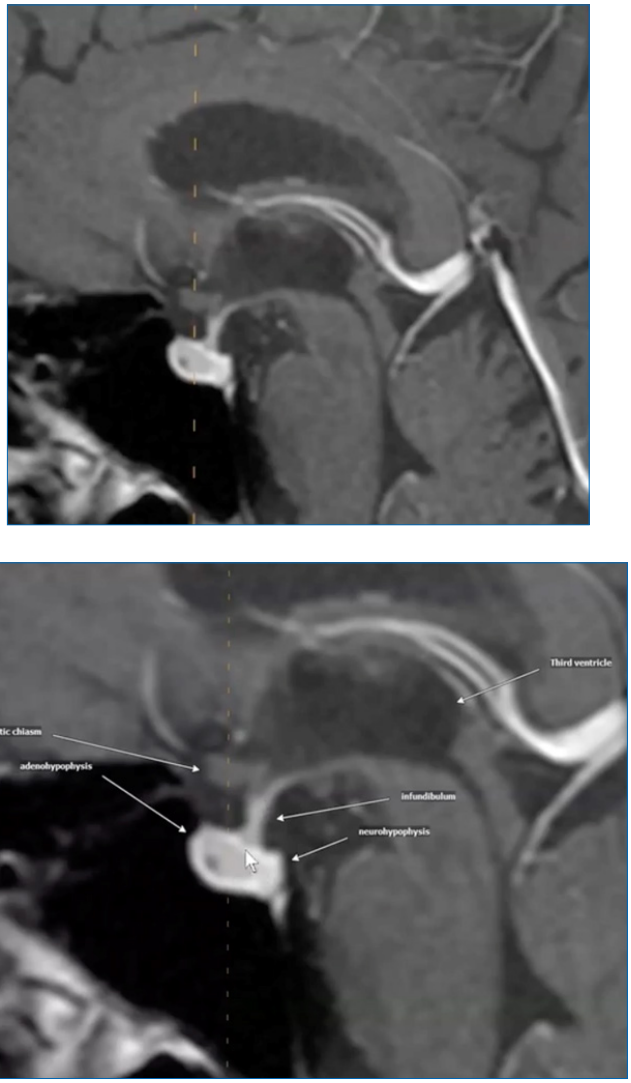
- Neurohypophysis
- 20% of the gland
- Direct extension of the hypothalamus
- Axon terminals from SON and PVN of hypothalamic neurons
- Hormone produced in hypothalamus, stored in pituitary



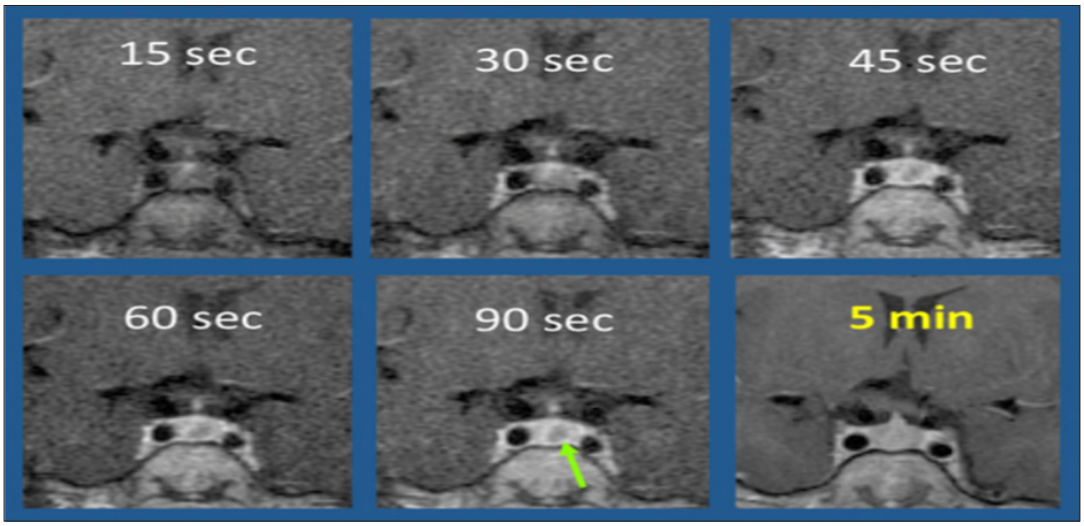
Pituitary Imaging - Normal Static Coronal



Pituitary Imaging - Normal Sagittal



Dynamic contrast-enhanced (DCE) imaging is a method for acquiring a series of MR images in rapid succession following the administration of contrast. Similar to CT, viewing the "wash- in" and "wash-out" of contrast on MRI may improve the detection and delineation of tumors and vascular lesions. An example is shown below:



Definition

- **Pituitary adenomas:** most are benign tumors of anterior pituitary cell origin [1,2,3].
  The most common pituitary lesion
- Pituitary adenomas are classified in several different ways depending on their properties:

Size: A microadenoma is equal to or < 1cm (10mm) in size; macro adenomas are bigger than one centimeter in size. Giant pituitary adenomas are bigger than 4 sm. MRI of the HP area is the imaging procedure of choice for diagnosis of pituitary adenomas and dynamic-contrast MRI is the imaging procedure of choice for pituitary microadenomas. The pituitary microadenoma usually does not grow. The macroadenomas- they grow- 0.6 mm/y. If the macroadenomas grow more than 1 mm/y and if they abut the chiasm- need surgery- TSS.

Aggressiveness: Nearly all pituitary adenomas are benign (non-cancerous) and slow-growing. Aggressive pituitary adenomas, grow quickly and are more likely to recur. Malignant pituitary carcinomas spread to other parts of the body, and are extremely rare(0.1%).

Hormone secretion: Pituitary adenomas that release excessive amounts of active hormone are called hormonally active or functional tumors. They are called non-functioning adenomas if they do not release an active hormone.

- Functional and nonfunctional tumors can both cause mass effects (most commonly from macro adenomas)

Epidemiology

In The United States

- Pituitary tumors represent anywhere between 10% and 15% of all intracranial tumors.
- Incidental pituitary tumors- incidentalomas are found in approximately 10-27% of autopsies and on MRI – 10-38%. Most of them are benign, non functioning microadenomas and 0.2% are incidentally found macroadenomas.

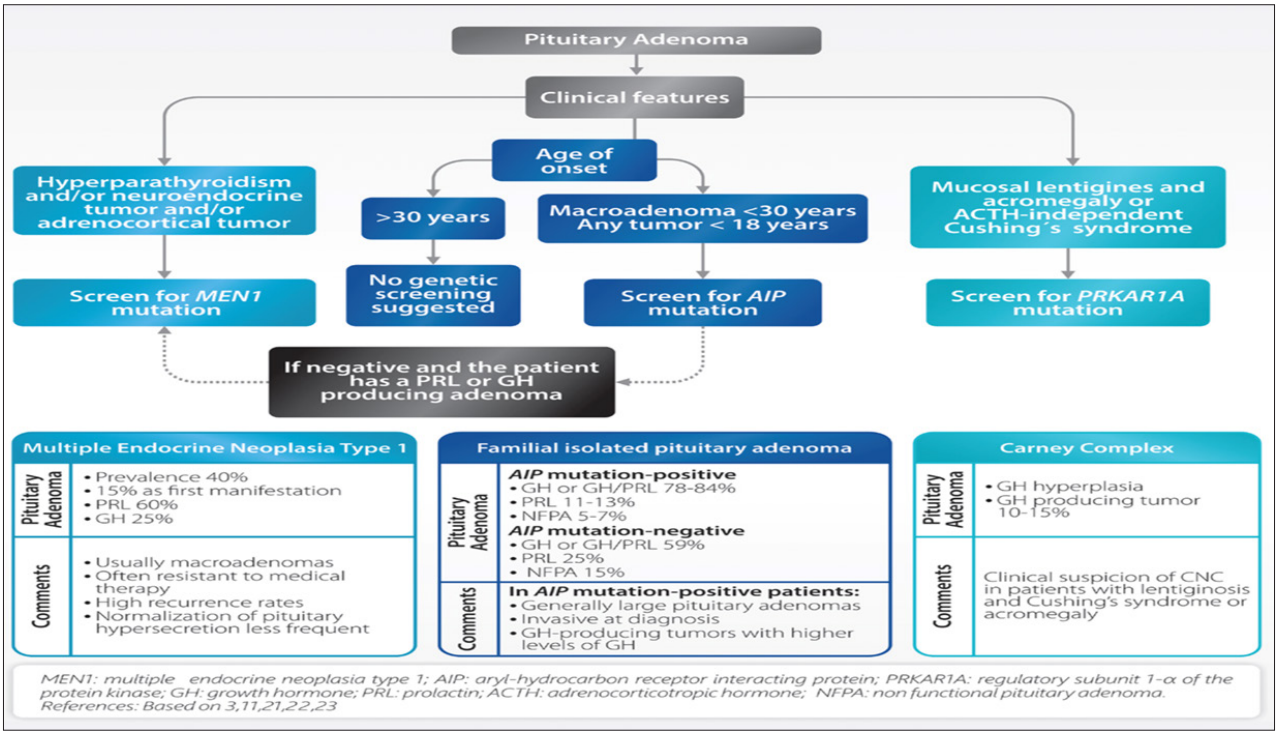
Pituitary adenomas present clinically as pituitary tumors much less likely – 1/1,000 to 1/10,000 people, which means that the majority of pituitary adenomas are found incidentally

Mortality/Morbidity

- Mortality rate related to pituitary tumors is low. Advances in medical and surgical management of these lesions and the availability of hormonal replacement therapies have contributed to successful management.
- Tumor recurrence is also a possibility.
- CNS metastases and, rarely, distant metastases occur with malignant pituitary tumors.

Etiology

- Most pituitary adenomas are sporadic(95%), meaning they are not inherited. They are usually monoclonal, arising from a single cell of pituitary gland so usually they secrete single pituitary hormone with few exceptions (or they are not secreting any pituitary hormones)
- There are cases of familial pituitary tumors, which is an inherited tendency to develop pituitary adenomas in (5%). However, these cases are uncommon[4].
- Multiple endocrine neoplasia type 1 (MEN 1) or MEN 4 are a rare conditions characterized by simultaneous tumors of the pituitary, pancreas and parathyroid glands. Pituitary adenomas develop in 25 percent of patients with MEN 1 or 4.



Genetic Causes of Pituitary Adenomas

Germline Mutations

- Aryl hydrocarbon interacting protein (AIP)
- Multiple endocrine neoplasia type 1 (MEN1)
- Carney complex (PRKAR1A)
- X-linked acromegaly/gigantism (GPR101)
- Neurofibromatosis type 1 (NF1)
- McCune Albright syndrome (GNAS)

Somatic Mutations

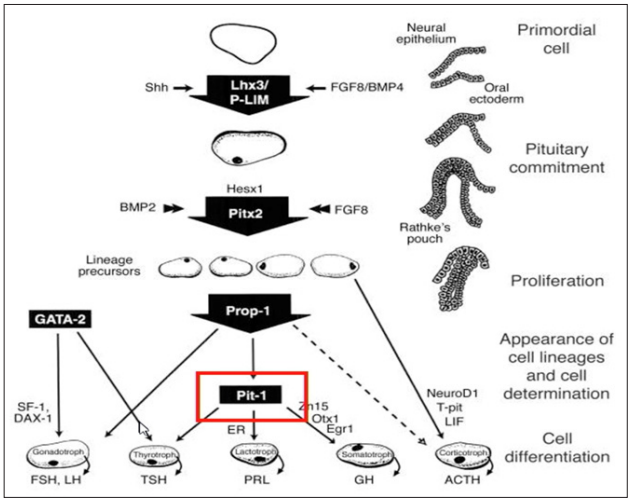
- Acromegaly (GNAS)
- Cushing disease (USP8)

The new WHO classification of pituitary adenoma based on histopathological criteria in addition to hormonal immunochemistry recognizes the role of other immunohistochemical markers including the pituitary transcription factors. Null cell adenoma for example needs immunochemically -negativity for pituitary transcription factors and hypophyseal hormones.The term atypical pituitary adenomas is no longer recommended.Assessment of tumor proliferation potential is based on mitotic count and KI-67 index(mitotic index)- how many cells are dividing, and clinical parameters like tumor invasion are recommended to be assessed in clinically aggressive adenomas.

What is the sellar lesion?

- Pituitary adenomas have been renamed as "pituitary neuroendocrine tumors" in the 5th WHO Classification of tumors of the central nervous system (CNS)
- In one surgical series, pituitary adenomas accounted for 91% out of 1,120 sellar masses

2017 World Health Organization classification of pituitary adenomas



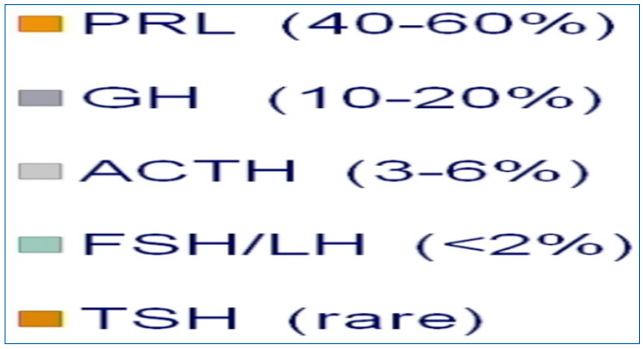
TSH,GH,PRL and plurinominal secreting tumors have the transcription factors PIT- 1.

ACTH secreting tumors have T-PIT transcription factor.

FSH/LH tumors have SF-1 and GATA-2 transcription factors and usually present with central hypogonadism.
Null cell tumors negative for transcription factors-no adeno hypophyseal linage of differentiation and present usually as central hypogonadisms

Metastatic PITNETS not anymore called Pituitary cancer

Functioning Pituitary adenomas frequency



AGGRESSIVE PITUITARY ADENOMAS[1]

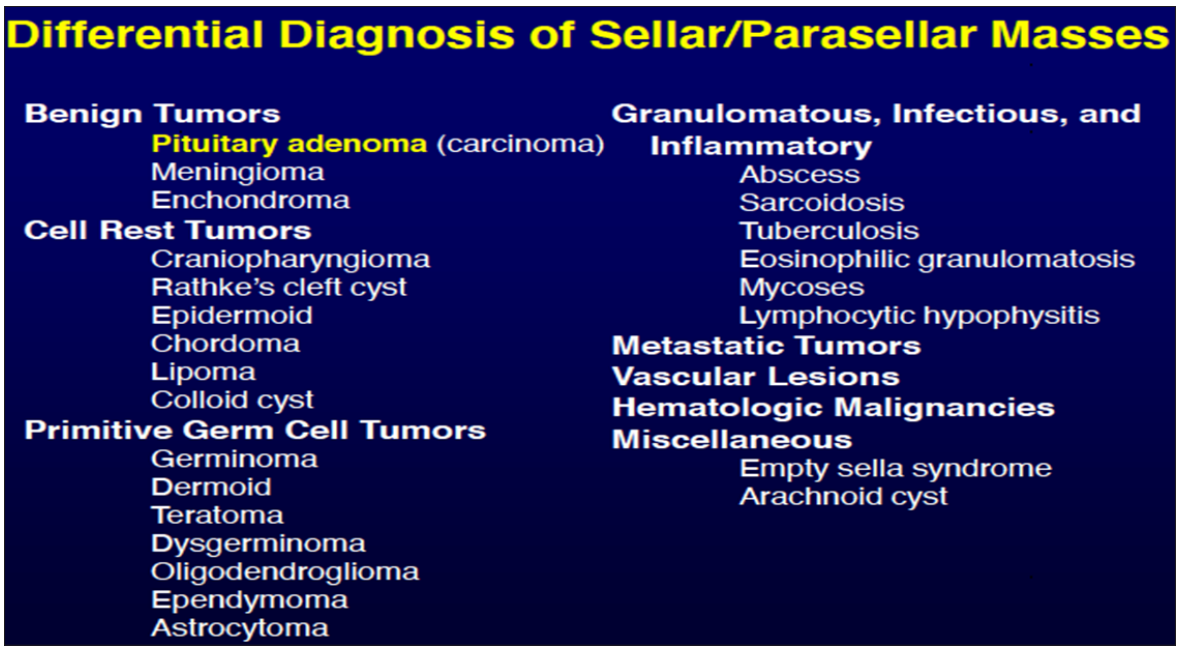
Type:

1. Sparsely granulated somatotroph adenomas
2. The lactotroph adenomas in men/resistant Prolactinomas
3. The Crook's cell adenomas- causing CD or 4
4. Silent corticotrope adenomas
5. PIT-1-positive adenoma

Clinical Behavior-invasive, large size, KI-67 >3%, p-53 immuno-positivity.
New Therapy for those tumors if not controlled-Temozolomide, Everolimus, Bevacizumab, Lapatinib

Pituitary adenomas/masses: questions to ask[1,2,3]

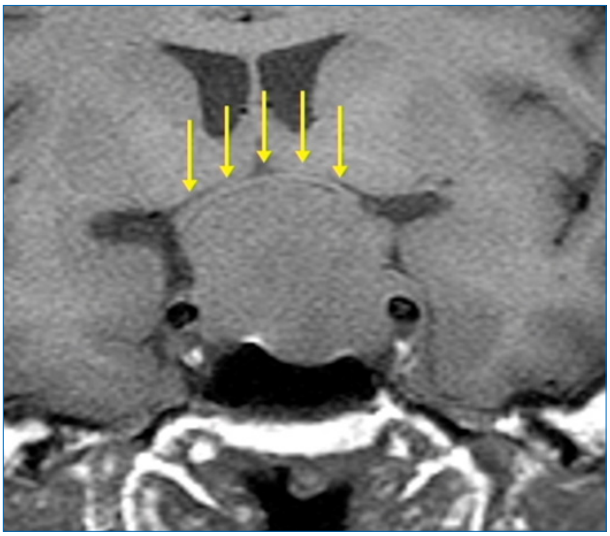
1. Does the adenoma cause mass effects- headache, decreased vision, cranial nerve palsy, numbness , etc.?
2. Is the adenoma hyper functional?
3. Does the adenoma cause decreased function of the HP gland?
4. Is the tumor metastatic/malignant? (usually, this means metastasis from cancer of the lung or the breast and extremely rare malignant primary tumors of the HP gland)
5. Is the adenoma growing?

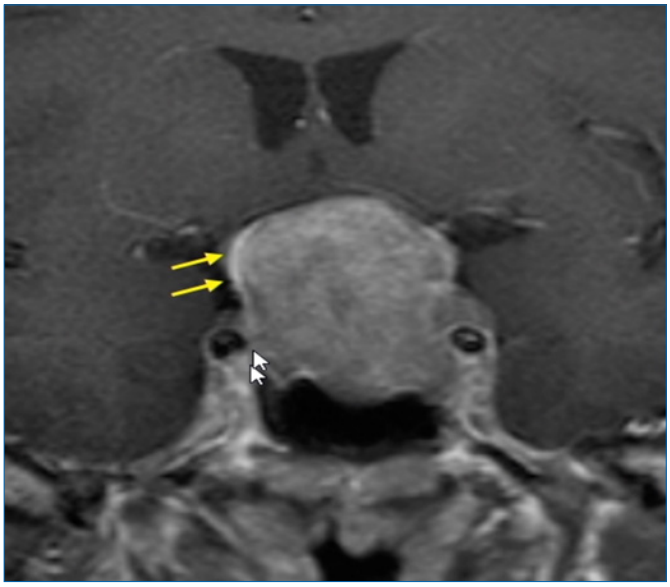


Case Presentation

- A 45-year-old male presents with a two month history of a visual defect in the left inferior visual field
- Further questioning reveals a longstanding history of headaches, with a recent increase in frequency and severity, fatigue, and a recent mild weight gain

Case Presentation : MRI



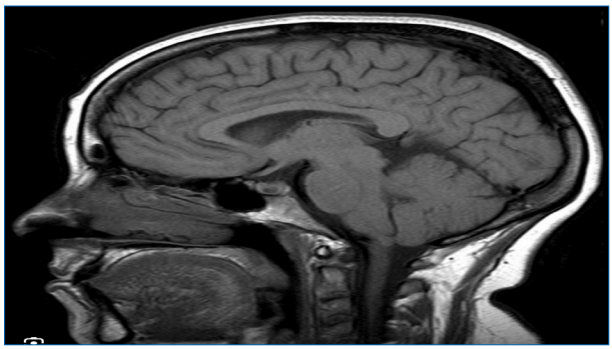


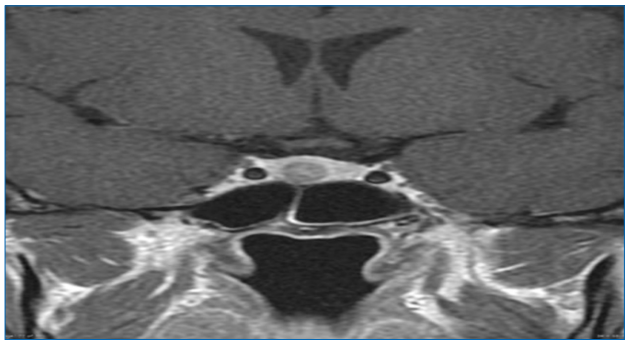
Case 1: Question

Based on the available data, this lesion most likely represents:

- A prolactinoma.
- A TSH-secreting pituitary adenoma.
- Lymphoma.
- A nonfunctioning pituitary adenoma.
- A gonadotropin-secreting adenoma.

MRI Pictures of pituitary microadenomas- Sagittal and coronal views





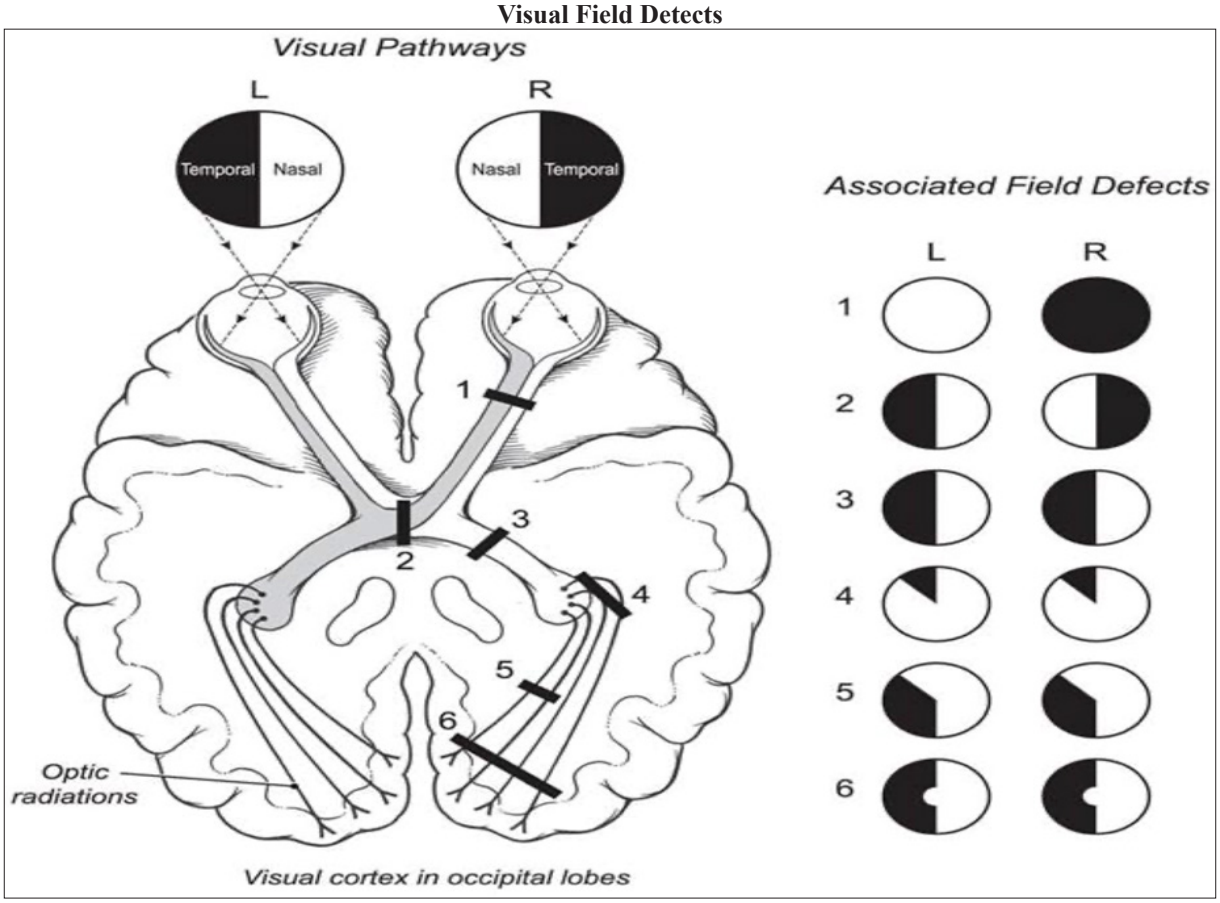
Pituitary Mass Effects

- Headaches
- Hypopituitarism Hyperprolactinemia
- Diabetes insipidus
- Visual loss
- Diplopia
- Facial numbness or pain
- Pituitary apoplexy

Intracranial Structures in Proximity to the Pituitary

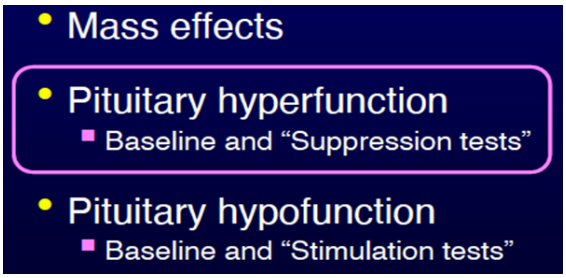
Direction of Expansion	Neighboring Structures	Symptoms of Compression
Upward	Optic pathways Hypothalamus Olfactory nerve	Visual field deficits, blindness Disturbed autoregulation Anosmia
Lateral	Cavernous sinus Internal carotid Oculomotor nerve Abducens, trochlear n. Ophthalmic nerve	Proptosis, eyelid edema Hemiplegia, altered LOC Ophthalmoplegia, ptosis, pupillary defects Ophthalmoplegia Facial pain, corneal anesthesia
Downward	Sphenoid sinus	Epistaxis, CSF rhinorrhea

Visual Field Detects



Approach to Pituitary Masses

Evaluate



Primary Assessment of Pituitary Adenomas[2,5]

1. Rule out pituitary hypersecretion- check PRL and IGF-1
2. Assess for CD only if you have signs and symptoms of the disease
3. Screen for hypopituitarism regardless of symptoms- check TSH, FT4, a.m. Cortisol/ACTH, LH /FSH/alfa SU, and Total testosterone in men. In premenopausal females, oligomenorrhea or amenorrhea raises the concerns of hypogonadotropic hypogonadism and requires investigation. Normal menses r/o central hypogonadism in female patients.No need to check LH/FSH in these cases. Abnormal initial hormonal testing needs further investigation and referral to an endocrinologist. In macroadenoma c/o hormonal assessment at 6 m, 1, 2 and 5 years, and in microadenoma if initial hormonal tests are fine, there is no need for repeat tests unless clinically indicated
4. Formal visual field assessment is needed if the pituitary tumor abuts or compresses the optic chiasm or is within 5 mm of the Optic chiasm
5. If patients do not need the surgical intervention of the pituitary tumor for mass effect or hypersecretion repeat imaging-MRI needs to be done in 6- months for pituitary macroadenomas and then in 1, 2 years and in 5– years and r/o hypopituitarism and in pituitary microadenoma- in 1- year, 2 and 5 years MRI and if no hypopituitarism initially no need to be r/o again unless growth or clinically indicated. Microadenomas-10% enlarge, macroadenomas-23% enlarge[5,6]
6. An important point to remember is that usually, pituitary tumors do not cause AVP-D. Usually metastasis/ craniopharyngioma etc. cause AVP-D. If given a case with AVP-D – do not think it is due to pituitary adenoma usually!

TSH-Secreting Adenoma [7]

- Very rare and accounts for less than 1% of all pituitary tumors
- Usually large at time of diagnosis and as a result patients also often have associated mass effects because inefficient TH synthesis
- These tumors may co-secrete TSH and prolactin or GH.
- Adenomas secreting TSH and growth hormone are equally common in men and women, whereas co-secretion of TSH and prolactin is approximately five times more common in women than in men.

TSH-Secreting Adenomas

Clinical manifestations

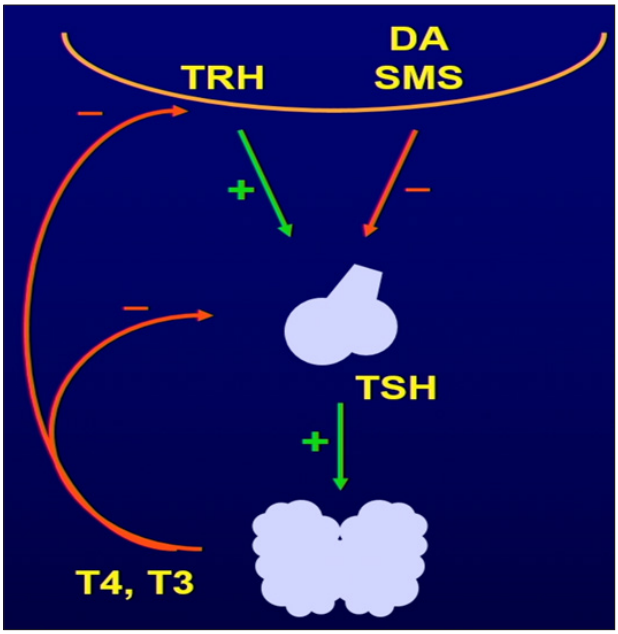
- Hyperthyroidism
- Goiter

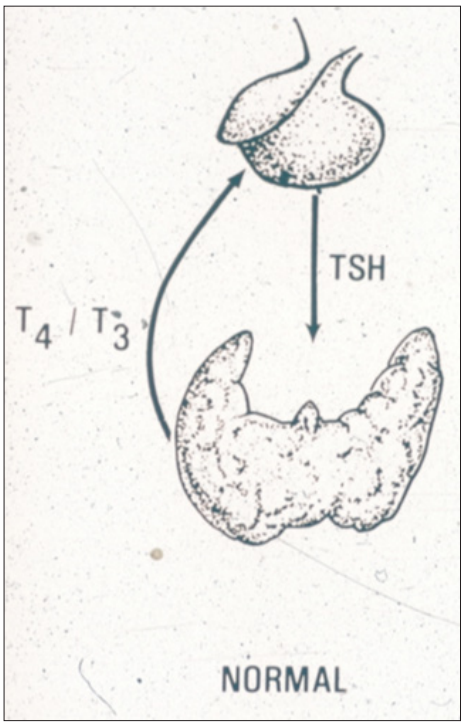
Diagnosis

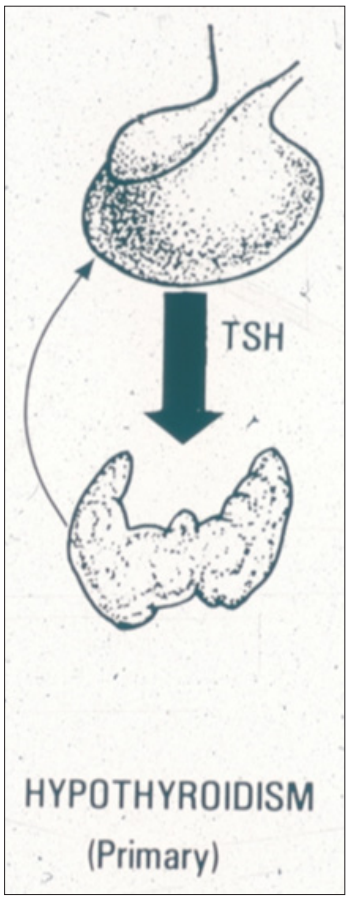
- Elevated FT4 levels
- Nonsuppressed TSH
- Macroadenoma
- Elevated α-subunit

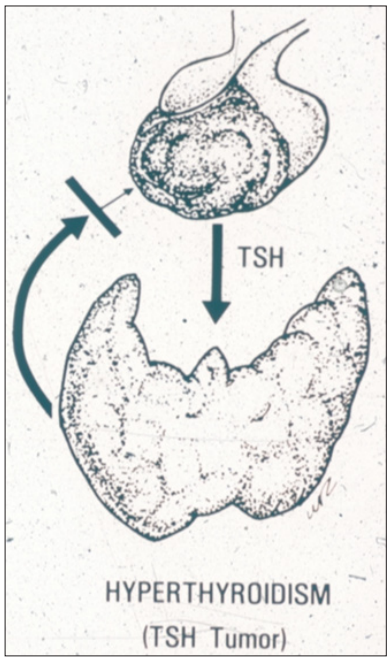
Therapy

- Surgery
- Somatostatin receptor ligands









TSH-oma

- Elevated T4 and non suppressed TSH
- Failure to suppress TSH after T3 suppression test (100% specificity with TSH <0.011)
- Elevated SHBG
- Increased ratio of alpha subunits/TSH

Clinical Presentation

A TSH-secreting pituitary adenoma should be suspected in patients with hyperthyroidism with diffuse goiter and no extrathyroidal manifestations of Graves' disease, who have high serum-free T4 and T3 concentrations and unsuppressed (normal or high) serum TSH concentrations, particularly in the presence of headache or clinical features of concomitant hypersecretion of other pituitary hormones (eg, symptoms of acromegaly, Prolactinoma) and or hyposecretion due to hypopituitarism.

Diagnosis

- High serum T4, T3, and "normal" or high TSH levels
- Measure alpha subunit of TSH , as approximately 50 to 85 percent of patients with TSH-secreting pituitary adenomas have high serum concentrations. A normal level makes the diagnosis less likely but does not exclude it.
- The subsequent finding of a pituitary macro adenoma by magnetic resonance imaging (MRI) is very strong evidence that the patient has a TSH-secreting pituitary adenoma, particularly in the presence of an elevated alpha subunit.

Differential DX- NL/High TSH and high FT4/TT3-Assay interference/TSH secreting pituitary adenoma and Thyroid hormone resistance:

1. THR- low SHBG
2. Low alfa SU to TSH ratio- less than- 1 in THR
3. Genetic testing available for THR
4. If a small TSH-secreting tumor is not visible on regular MRI obtain Dynamic MRI- rare cases

Treatment

- The initial treatment of a TSH-secreting pituitary adenoma is trans sphenoidal resection of the tumor, which is the most appropriate and definitive therapy for patients with TSH-secreting pituitary adenomas after initial control of the disease with SRL and if needed Methimazole.
- With this approach most patients with micro adenomas (≤10 mm) will be cured. Approximately half of patients with macro adenomas will require additional medical therapy for residual disease.
- Second line -iSRLs
- Medical therapy (with somatostatin Receptor ligands for residual disease after surgery or if the surgery is contraindicated to suppress the TSH secretion from the TSH secreting tumor
- In addition, somatostatin receptor ligands reduces the size of the tumor prior to resection.

Treatment of TSH-omas with Octreotide & Lanreotide

TSH & a-subunit normalization	90%
T4/T3 normalization	90%
Goiter size reduction	30%
Vision Improvement	70%
Tumor shrinkage	40%

True escape, Resistance, D/C of therapy due to side effects - minority of cases

Clinically Silent Pituitary Tumors

Tumor Type	Number (n=2012)	Frequency
Gonadotroph	865	43.0%
Null cell	678	33.7%
Corticotroph	111	5.5%
Lactotroph	34	1.6%
Somatotroph/Acidophil	21	1.0%
Thyrotroph	18	0.9%
Plurihormonal	36	1.8%
Unclassified	33	1.6%

Gonadotropin-Secreting Adenomas

Clinical manifestations

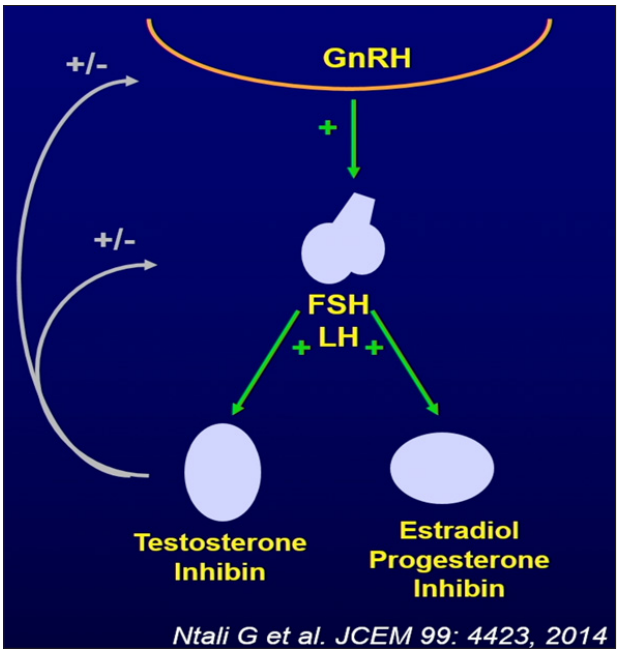
- Usually nonfunctional, asymptomatic
- Ovarian cysts,
- hyperstimulation syndrome
- Infertility
- Sexual dysfunction
- Macro-orchidism
- Precocious puberty
- Macroadenoma

Diagnosis

- Differentiate from primary hypogonadism, menopause
- Nonsuppressed LH/FSH in setting of elevated gonadal steroids
- Elevated alpha subunit

Therapy

- Surgery



FSH/LH secreting adenomas[8,9]

Pituitary adenomas that are clinically nonfunctioning or "silent"-

Gonadotrophic adenomas are the most common type of pituitary macro adenoma. FSH and LH are complex hormones with 2 units that must be glycosylated and then combined in an appropriate ratio – which is not a very efficient process in making biologically active hormones by this adenoma; this is why they are usually clinically non-functional, but they stain positive for these hormones or their subunits in immunostaining

- Although gonadotrophic adenomas are considered to be "nonfunctioning", most do produce intact gonadotropins or their subunits. However, these adenomas are typically poorly differentiated and inefficient producers/secretors and do not raise serum gonadotropin concentrations. Thus, they are usually clinically "silent" and cannot be distinguished from other clinically nonfunctioning adenomas until immunohistochemistry is performed after pituitary surgery. As a result, by the time a gonadotrophic adenoma produces supernormal serum concentrations of intact gonadotropins or their subunits, they become macroadenomas
- FSH/LH pituitary adenomas are typically asymptomatic and are treated similarly to nonfunctioning adenomas because they do not secrete enough FSH or LH to produce a clinical syndrome.
- Usually, they are macro adenomas and are diagnosed because of mass effect or because they are causing central hypogonadism, GH deficiency, or panhypopituitarism because of the compression of the normal Hypophyseal / HP/gland

Clinical Presentation & Diagnosis

- Most often diagnosed when mass effects are present
- The three most common presentations include the following :
- Neurologic symptoms, most commonly visual symptoms; less commonly headache.
- A pituitary mass that is discovered as an incidental finding when an imaging procedure is done for reasons other than pituitary symptoms or disease.
- Pituitary hypofunction due to compression of normal pituitary tissue by the adenoma.
- The most common clinical hormone deficiency is impaired secretion of gonadotropins resulting in secondary hypogonadism with infertility and sexual dysfunction and GH deficiency
- Patients suspected of having these adenomas should undergo pituitary MRI as well as testing of pituitary function

A few of these gonadotropinomas do secrete an increased amount of biologically active hormones, usually FSH, but might be FSH and LH, and are known as functioning gonadotrophin-producing adenomas (FGA). They are usually macro adenomas and women have elevated estradiol (males have elevated testosterone) and normal not suppressed levels of FSH and LH.

These FGA can result before puberty in isosexual central precocious puberty in children of both sexes.

In female patients, they can cause ovarian hyperstimulation with ovarian cysts, menstrual irregularities(most often), infertility in premenopausal women. In men they cause testicular enlargement , erythrocytosis and sexual dysfunction.

Treatment

- Trans sphenoidal resection
- Confirmation of diagnosis with immunohistochemistry after pituitary surgery

Natural History of Untreated Pituitary Incidentalomas

	Microadenomas	Macroadenomas
Total	229	419
Enlarged	23 (10%)	96* (23%)
Decreased	17 (7%)	51 (12%)
No Change	189 (83%)	272 (65%)
Yrs followed	0.6-15.0	0.6-12

Regrowth of Pituitary Adenomas Following Surgery with and without Postoperative Radiotherapy when Tumor Status Known Postoperatively

- No visible tumor postoperatively
  - RT in 14, Regrowth in 1 (7%)
  - No RT in 615, Regrowth in 86 (14.0%)
- Visible tumor postoperatively
  - -RT in 339, Regrowth in 38 (11.2%)
  - -No RT in 487, Regrowth in 244 (50.1%)

Clinically nonfunctioning pituitary adenomas-Transsphenoidal surgery(TSS)[8]

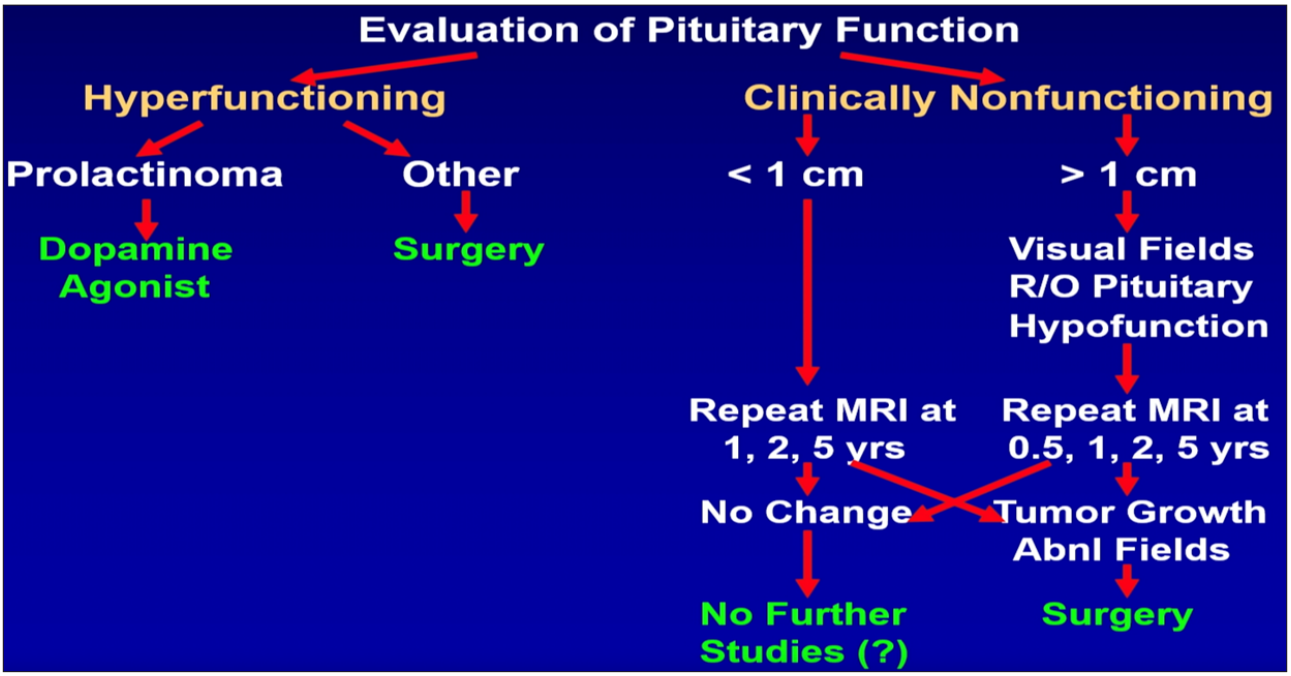
Tumor Debulking can be achieved after TSS in more than 90% of the patients in experthands.

Vision improves in 75-90% of the patients and headache improves in 65% of the patients.

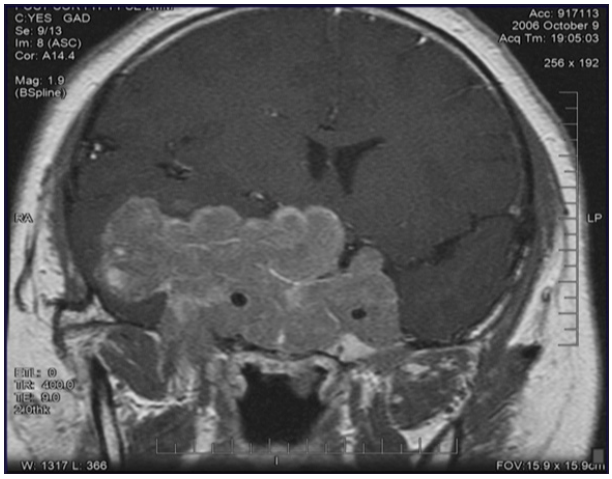
Recovery of preoperative hormone deficiency occurs in 30-40% of the patients.

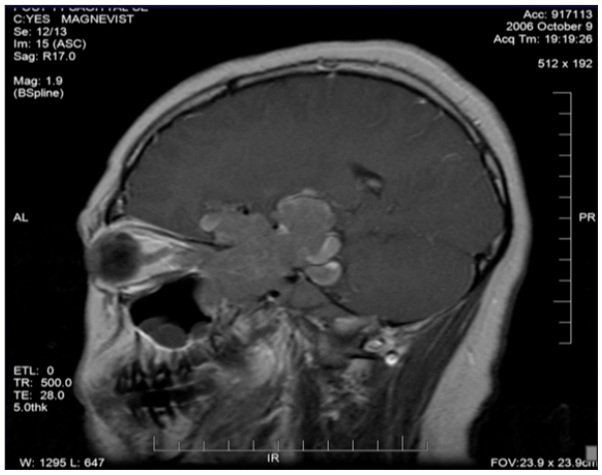
Development of postoperative new hormonal deficiency occurs in 5-10 % of the patientsRadiation therapy is effective in achieving tumor control in > 90% of patients with residual or enlarging tumors after TSS. RT is not given routinely after TSS nowadays, but if there are visual abnormalities or hypopituitarism.

Flow Diagram for Pituitary Incidentalomas



Giant Prolactinoma



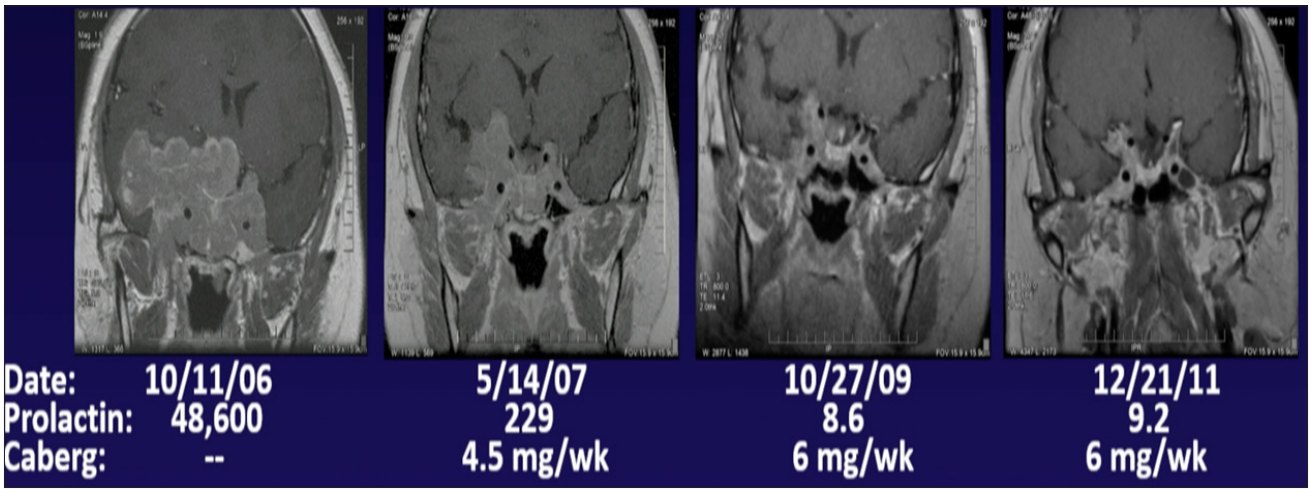


- Presentation: Primary Amenorrhea in a 17 year old woman
- Prolactin 48,600 ng/mL

Surgery for "Giant" Prolactinomas

- Giant pituitary adenomas defined as tumors > 4 cm in diameter
- Operative cures - none
- Operative complications high
- Pia et al: 77 pts: 8 deaths, 4 visual loss, 8 oculomotor palsies, 15 DI, 14 mental deterioration, 5 CSF fistulas
- Guidetta et al: 21 case: 2 deaths, 4 DI, 1 hemiparesis, 1 "hypothalamic failure"

Response of Gaint Prolactinoma to Cabergoline



Pituitary Adenomas:
Therapeutic Considerations

Treat symptoms related to mass effects.

- Restore or preserve vision
- Neurologic improvements - cranial nerves, headaches

Correct pituitary hyperfunction.

- Aim for biochemical cure

Medical hormone replacement for hypopituitarism.

Hypopituitarism

Treatment based on correcting hormone deficiencies. Adrenal - hydrocortisone or prednisone. Use lowest dose possible.

- Stress dose coverage
- Mineralocorticoid replacement not necessary.

Thyroid - levothyroxine, after adrenal replacement

- **Remember TSH cannot guide Rx.
- Gonadal - Men require testosterone, women may require estrogen-progestin replacement. Gonadotropins for fertility.
- Growth hormone – Need provocative testing. Can treat with rhGH.
- Prolactin - no replacement available or required.
- Posterior pituitary – desmopressin (DDAVP).

Pituitary Incidentaloma
Indications for Surgery

- Visual field deficits or other visual abnormalities
- Lesion abutting on optic nerves on MRI
- Pituitary apoplexy

- Hormone hypersecretion (except PRL)
- Clinically significant growth
- Development of pituitary insufficiency
- Lesion close to optic chiasm and plans to become pregnant
  Unremitting headache

Summary:Take-Home Messages

Evaluation of Pituitary Mass

- Differential diagnosis
- Pituitary hyperfunction
- Pituitary insufficiency
- Mass effects

Management of Pituitary Mass

Surgery

-mass effects
- hormone excess
- diagnosis

Medical

- prolactinoma*
- GH-secreting

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