MEDICINE-
ENDOCRINOLOGY
NEET-SS

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PITUITARY TUMOR SYNDROMES

Clinical manifestations

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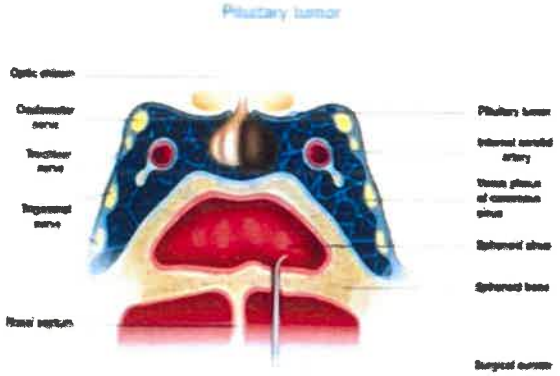
Sellar masses may present with various clinical manifestations depending on :

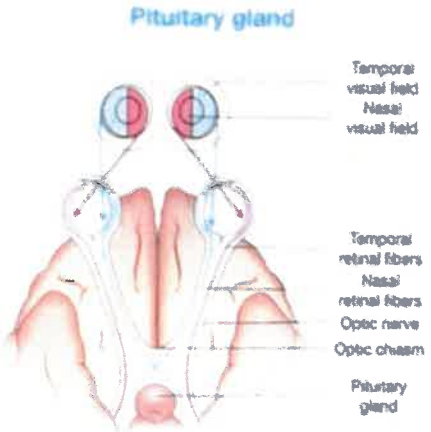
- Anatomic location of the mass.
- Extension.
- Functionality.



Suprasellar extension :

Compression of optic chiasma :

- Dorsal sellar diaphragm → Area of least resistance → Suprasellar extension → Compression of optic chiasma.
- Leads to :
  - Loss of red perception.
  - Bitemporal hemianopia.
  - Superior or bitemporal field defect.
  - Scotoma.
  - Blindness.



- Ophthalmologic evaluation :
  - Visual acuity : Snellen chart.
  - Visual field : Bedside by confrontational testing, goldmann perimetry, Amsler grid, automated quantitative perimetry.

Headache :

- Due to ↑ intrasellar pressure which stretches the dural plate.
- Headache severity does not correlate with the size of the adenoma or the presence of suprasellar extension.

Invasion through palatal floor :

- Bony invasion may occur through the sellar floor to the sphenoid sinus.
- Aggressive tumors rarely invade the palate roof and cause nasopharyngeal obstruction, infection and CSF leakage.

Pituitary stalk compression :

Pituitary stalk compression by intrasellar mass → Compress the portal vessels → Disrupting pituitary access to hypothalamic hormones and dopamine → Hyperprolactinemia (Even with a hormonally inactive mass) → Later, concurrent loss of other pituitary hormones.

Stalk section phenomenon :

Seen with trauma, whiplash injury with posterior clinoid stalk compression, skull base fractures.

Lateral mass invasion :

- Lateral mass invasion → may impinge on the cavernous sinus → Cranial nerve III, IV, VI, V-1 (Ophthalmic), V2 (maxillary) palsies.
- Diplopia, ptosis, ophthalmoplegia and decreased facial sensation.

Temporal and frontal lobe involvement :

Uncinate seizures, personality disorders and anosmia (Rare).

Hypothalamic involvement :

- Precocious puberty or hypogonadism.
- Diabetes insipidus (Adypsic).
- Sleep disturbances.
- Dysthermia.
- Appetite disorders.

Features of sellar mass lesions :

Impacted structure	Clinical impact.
Pituitary gland	Hypogonadism.
	Hypothyroidism.
	Growth failure, adult growth hormone deficiency.
	Hyposdrenalism.
	Hyperprolactinemia (stalk compression).
Optic chiasma	Loss of red perception.
	Bitemporal hemianopia.
	Superior or bitemporal field defect.
	Scotoma.
	Blindness.

Classification of pituitary tumors

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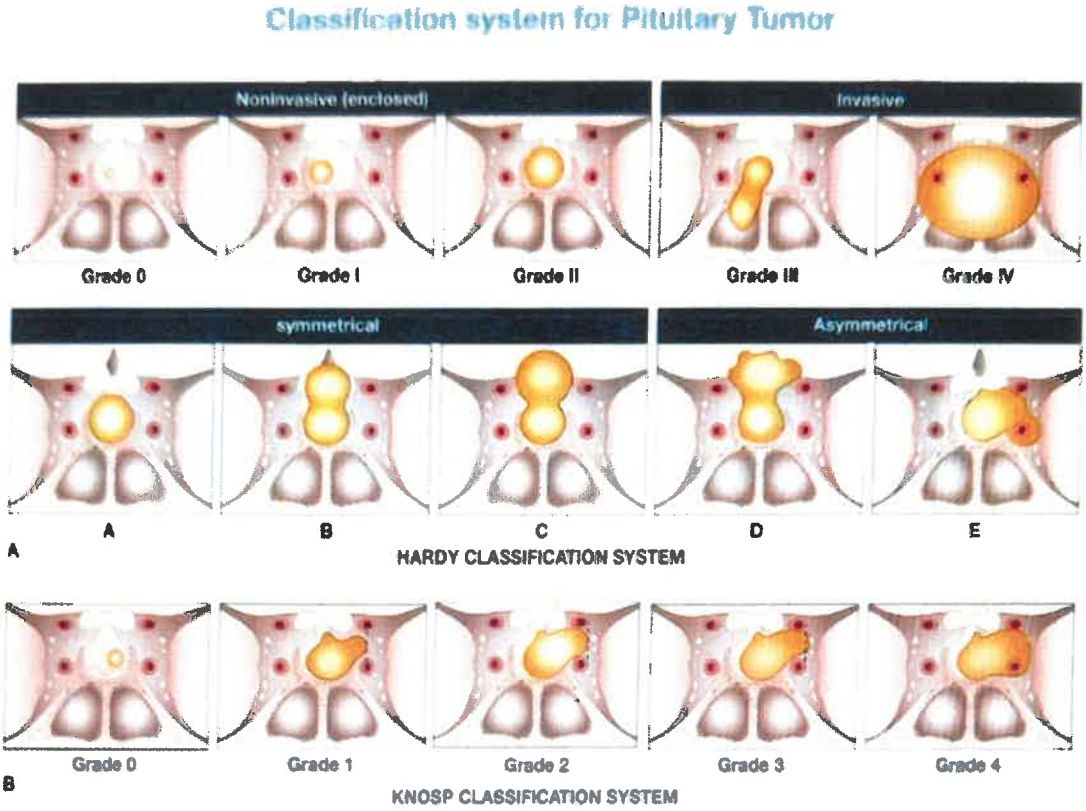
Hardy's : Sellar and suprasellar extension.

Knosp's : Cavernous sinus invasion.

Elster.



Hardy classification :

Non-invasive vs invasive :

Grade 0 : Tumor within the sella and contour maintained.

Grade I : Within the sella but slight bulge (+).

Grade II : Enlarged but confined to the sella.

Grade III : Localised invasion.

Grade IV : Diffuse destruction.

Based on suprasellar extension :

A : Extension towards the suprasellar skull.

B : Extension upto the 3rd ventricle.

C : Entire 3rd ventricle is involved.

D : Intracranial extradural involvement.

E : Extracranial extradural involvement.

Knosp's classification :

With respect to cavernous sinus invasion.

Grade 0 : No invasion.

Grade 4 : Encasement of internal carotid artery.

Note :

Encasement : Internal carotid artery involved ≥ 180°.

Abutment : Internal carotid artery involved ≤ 180°.

Evaluation 00:24:16

Ophthalmologic evaluation :

- Bitemporal hemianopia :
  - more common.
  - more pronounced superiorly.
  - D/t compression of the ventral optic chiasma, nasal ganglion cell fibres.
- Homonymous hemianopia : Postchiasmal compression.
- monocular temporal field loss : Prechiasmal compression.

Laboratory investigation :

To assess functionality and deficiency :

- Serum prolactin (PRL)/basal prolactin.
- 8 AM cortisol/ 24-h urinary free cortisol (UFC) and/or overnight oral dexamethasone (1 mg) suppression test.
- Thyroid function tests : T4, TSH.
- Na/K.
- Insulin-like growth factor (IGF1).
- LH/FSH.

Screening tests for functional pituitary adenomas :

	Test	Comments
Acromegaly	Serum IGF-1. Oral glucose tolerance test with GH obtained at 0, 30, and 60 min.	Interpret IGF-1 relative to age- and sex-matched controls. Normal subjects should suppress growth hormone to <1 µg/L.
Prolactinoma	Serum PRL	Exclude medications. MRI of the sella should be ordered if PRL is elevated.

Cushing's disease	24-h urinary free cortisol Dexamethasone (1 mg) at 11 P.M and fasting plasma cortisol measured at 8 AM. Late night salivary cortisol ACTH assay.	Ensure urine collection is total and accurate. Normal subjects suppress to <5 μg/dL. Distinguishes adrenal adenoma (ACTH suppressed) from ectopic ACTH or Cushing's disease (ACTH normal or elevated).
Gonadotropinoma	Baseline FSH, LH, free α subunit, ovarian hyperstimulation, Estrogen (females), testosterone (males). TRH stimulation test with assays for LH, FSH, free α subunit, free LHβ, free FSHβ subunits.	Rare; more commonly nonfunctioning adenomas. Consider screening for hypopituitarism ; Some gonadotropinomas exhibit an inappropriate gonadotropin response to TRH.
TSH-producing adenoma	Free T_4, free T_3, TSH, free α subunit.	Key feature is an inappropriately normal or high TSH in the setting of elevated free T_4 and T_3

Histologic evaluation :

Immunohistochemical staining after transsphenoidal surgery for :

- Hormones : Hormone studies are equivocal and in cases of clinically non-functioning tumors.
- Cell-type specific transcription factors.

Treatment

00:30:45

Usually pituitary adenomas are benign and slow growing tumors.

Goals :

- Normalization of hormone secretion.
- Amelioration of symptoms and signs.
- Shrinkage of tumor masses.
- Relief of adjacent structure compression.
- Restoration of pituitary function.
- Prevention of recurrence.

Treatment options :

- Transsphenoidal surgery.
- Stereotactic radiotherapy.
- Novel therapeutic agents.

Transsphenoidal surgery :

- Desired surgical approach for pituitary tumors.
- Transcranial approaches : For invasive suprasellar mass surrounding the frontal or middle fossa or the optic nerves or invading posteriorly behind the clivus.
- Intraoperative microscopy helps in visual distinction between adenomatous and normal tissue.

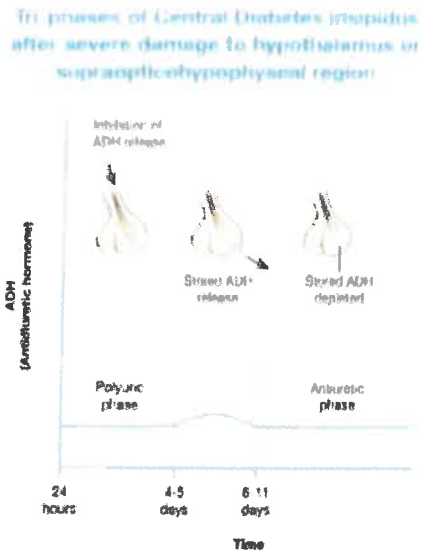
- Surgical decompression and resection done in cases of :
  - Expanding pituitary mass.
  - Asymptomatic/headache.
  - Progressive visual field defects.
  - Cranial nerve palsies.
  - Hydrocephalus.
  - Intrapituitary hemorrhage/apoplexy.
- Whenever possible, the pituitary mass lesion should be selectively excised.
- Total hypophysectomy may be indicated if :
  - No hypersecreting mass lesion is clearly discernible.
  - Multifocal lesions are present.
  - Remaining non-tumorous pituitary tissue is necrotic.

Complications :

- Operative mortality rate is ~1%
- Transient diabetes insipidus and hypopituitarism : Occur in up to 20%.
- Cranial nerve damage.
- Nasal septal perforation.
- Visual disturbances.
- CSF leaks occur in 4%.
- Less common complications : Carotid artery injury, hypothalamic damage and meningitis.

Post operative diabetes insipidus (DI) :

Transient DI (25%)	Permanent (20%)	Triphasic
• Within 24-48 hours. • Resolves in few days. • Due to axonal shock. • Temporary dysfunction.	• High stalk injury. • Closer the lesion to the magnocellular cell bodies in the hypothalamus, the more likely that the hypothalamic cell bodies will degenerate.	• Complete transection of tract. • 1st phase of DI : 5-7 days due to axonal shock. • 2nd phase : Antidiuretic phase of SIADH lasts for 2 days to 2 weeks. • 3rd phase of chronic DI : After the AVP stores are depleted.



Radiation therapy :

- Primary therapy/adjunct to surgery or medical therapy.
- Because of its relatively slow onset of action, radiation therapy is usually reserved for post surgical management.
- Types :
  a. Conventional radiation : Total of <50 Gy (5000 rad) is given as 180-cGy (180- rad) fractions divided over ~6 weeks.
  b. Stereotactic radiosurgery : Large single high-energy dose from a cobalt-60 source (Gamma Knife), linear accelerator or cyclotron.

Complications :

- Transient nausea, weakness, alopecia, loss of taste and smell.
- ≥50% of patients develop loss of GH, ACTH, TSH and/or gonadotropin secretion within 10 years, usually due to hypothalamic damage.
- Optic neuritis : Approximately 2% cases.
- Risk of developing a secondary tumor after conventional radiation is 1.3% after 10 years and 1.9% after 20 years.

medical management :

- Prolactinomas : Dopamine agonists.
- Acromegaly : Somatostatin receptor ligands (SRLs) and GH receptor antagonist.
- TSH-secreting tumors : SRLs and occasionally dopamine agonists.
- ACTH-secreting tumors : SRLs, adrenal-directed therapy.

Sellar masses

00:39:23

In hypothalamic regions :

- Anterior and preoptic hypothalamic regions : Paradoxical vasoconstriction, tachycardia and hyperthermia.
- Ventromedial hypothalamic nuclei involved : Hyperphagia and obesity seen.
- Preoptic nuclei : Central osmoreceptors → Polydipsia and hypodipsia.
- Central hypothalamus : Stimulate sympathetic neurons → ↑Catecholamine and cortisol levels → Cardiac arrhythmias, hypertension and gastric erosions.

Craniopharyngiomas :

- Benign, locally invasive, suprasellar cystic masses.
- Often large, cystic, and locally invasive.
- Derived from Rathke's pouch.
- Partially calcified : Seen on skull x-ray and CT images.
- Over 60% arise from within the sella, and others arise from parasellar cell rests.

Epidemiology :

- more than half of all patients present <20 years.
- Bimodal peak :
  - 5-14 years of age.
  - Later at 50-74 years.
- 80-90% of all pituitary tumors in children : Craniopharyngioma.
- Comprises of 15% of all intracranial tumors in children.

Clinical features :

- Hypopituitarism (90% cases).
- Diabetes insipidus (10%).
- About half of affected children present with growth retardation.
- When intra-sellar, can be distinguished from pituitary adenomas by separate visible rim of normal pituitary tissue.
- Cystic mass filled with cholesterol-rich viscous fluid which may leak into the CSF → Aseptic meningitis.

Types :

i. Adamantinomatous form :
   - WNT/ beta catenin mutation.
   - Seen in children.

ii. Papillary forms :
   - BRAF mutation.
   - Seen in adults.

Investigations :

- MRI head with contrast :
  - Neuroimaging of choice.
  - MRI is generally superior to CT for evaluating cystic structure and tissue components of craniopharyngiomas.
- CT scan : To define calcifications and invasion into surrounding bony structures and sinuses.

Treatment :

- Transcranial or transsphenoidal surgical resection followed by postoperative radiation of residual tumor.
- In the absence of radiotherapy, 75% of craniopharyngiomas recur and 10-year survival is <50%.
- BRAF inhibitors (Dabrafenib or vemurafenib) either alone or in combination with MEK inhibitors (Trametinib or cobimetinib).
  Craniopharyngiomas (Particularly papillary) are associated with activated BRAF V600E mutations.

Post operative complications :

- Hyperphagia and obesity post surgery.
- Narcolepsy.
- Diabetes insipidus, adipsic hypernatremia.
- Recurrence (20%).

Rathke's cysts :

- Developmental failure of Rathke's pouch obliteration.
- Usually anterior and intermediate lobes are involved.
- Small (<5 mm) cysts entrapped by squamous epithelium and are found in ~20% at autopsy.
- Do not grow usually.

- Often diagnosed incidentally.
- 1/3rd present in adults with compressive symptoms : Diabetes inspidus/hyperprolactinemia.

Pituitary metastases :

- Blood-borne metastatic lesions.
- Usually from breast cancer (m/c), lung, gastrointestinal, primary or metastatic lymphoma, leukemias and plasmacytomas.
- Almost exclusively in the posterior pituitary → Leads to DI.
- Diagnosis : Histologic examination of excised tumor tissue.

Hypothalamic hamartomas :

- From astrocytes, oligodendrocytes, and neurons.
- May overexpress GnRH, GHRH, CRH.
- C/F :
  - Laughing-associated seizures (Gilastic seizure).
  - Pallister-Hall syndrome :
    Craniofacial abnormalities, imperforate anus, cardiac, renal, and lung disorders, and pituitary failure.
    mutations in the carboxy terminus of the GLI3 gene.

Germinomas or GCT :

- Extra sellar tumors arising from pineal and neurohypophysis region.
- Infancy, 2nd decade.
- Clinical features :
  - DI.
  - Short stature.
  - Puberty or movement disorders.
  - Serum HCG, CSF HCG, AFP↑.
- Treatment :
  - Radiotherapy.
  - Radiotherapy + Chemotherapy.
- Associations : ↑HCG leads to gonadotropin independent isosexual puberty (GISP) in males.
- Any enlargement in pineal gland after 1 year should arise suspicion of pineal mass lesion.

One liners :

- Sella chordomas : Bony clival erosion, local invasiveness and calcification.
- Arachnoid cysts : Isointense with CSF.
- Meningiomas : Isodense on T1 & T2 + Calcification or bony erosion.
- Histiocytosis X : DI, exophthalmos, and punched-out lytic bone lesions (Hand Schuller-Christian disease) with characteristic axillary skin rash.
- Hypothalamic gliomas : 1/3rd associated with neurofibromatosis.
- Germinomas, embryonal carcinomas, teratomas and choriocarcinomas : Arise in parasellar region and produce hCG.
- Pituitary infections : Acute pituitary abscesses and perisellar arachnoiditis seen as isointense central cavity with surrounding ring enhancement.
- Pituicytoma :
  - Benign central noninvasive suprasellar glial cell tumor.
  - Stains for vimentin, S100 protein, and glial fibrillar acidic protein.
- Hemochromatosis and hemosiderosis : Predominantly gonadotroph cell damage.

Hypophysitis :

- Pituitary stalk thickening.
- Clinical features :
  - Headache, visual field impairment, hyperprolactinemia and pituitary deficiency.
  - Secondary hypoadrenalism (ACTH deficiency).
  - Followed by hypothyroidism, hypogonadism, and GH or PRL deficiency.
- MRI reveals a pituitary mass, often indistinguishable from an adenoma.
- Treatment :
  - High dose glucocorticoids is the mainstay, often resolving the sellar mass and improving endocrine dysfunction.
  - Recurrences are reported in over 40%.

Lymphocytic hypophysitis :

- During or shortly after parturition (Last month of pregnancy or during the first 2 months postpartum).
- 15% in males.
- Lymphocytic and plasma cell pituitary infiltrate.
- Circulating anti-pituitary antibodies present.
- Secondary adenohypophyseal cell atrophy can occur leading to empty sella.
- D/D : Sheehan's syndrome.

- Pathologic criteria for diagnosis : Islands of anterior pituitary cells surrounded by diffuse lymphocytic (T-cell and B-cell) infiltrates.
- Raised ESR.
- In 1/3rd of patients, other autoimmune conditions (Thyroiditis, hypoadrenalism, parathyroid failure, atrophic gastritis, SLE or Sjögren syndrome) seen.
- Spontaneous resolution.
- Treatment :
  - Pituitary hormone replacement.
  - Transsphenoidal or endoscopic surgical resection : To confirm a tissue diagnosis or relieve compression symptoms.

Granulomatous hypophysitis :

- Females predominated (But not associated with pregnancy).
- Histology : Chronic inflammation and granuloma with histiocytes and multinucleated giant cells.
- Suprasellar extension occurs in about 60%.
- Associated with sarcoidosis, Takayasu disease.

Xanthomatous hypophysitis :

- Equal frequency in both sexes.
- Lipid-laden macrophages.
- MRI : Highly cystic lesion, possibly reflecting an inflammatory response to a ruptured pituitary cyst.

Note :

IgG4-related hypophysitis : Associated with retroperitoneal fibrosis, pancreatitis, and thyroid, lung and meningeal involvement.

Immune checkpoint inhibitor induced hypophysitis :

- Cytotoxic T-lymphocyte antigen 4 (CTLA4) also expressed on pituitary tissue causes local complement activation.
- M/C endocrine deficit : Secondary adrenal insufficiency.
- Ipilimumab induced hypophysitis :
  - Male : Female ratio is 2 : 1.
  - 10% incidence.
- Treatment :
  - High-dose steroids.
  - Azathioprine.

PITUITARY ADENOMA BASICS AND PROLACTINOMA

Pituitary adenomas

00:00:21

Consists of 15% of all intracranial neoplasms.

Prevalence :

- 80/100,000.
- Autopsy shows 25% have microadenoma.
- Pituitary imaging shows 10% of cases.

Pathogenesis :

- Benign neoplasms, monoclonal in origin.
- Arise from one of the five anterior pituitary cell : Lactotrope (PRL), somatotrope (GH), corticotrope (ACTH), thyrotrope (TSH) or gonadotrope (LH, FSH).
- Plurihormonal tumors express various combinations.
- One third are clinically non-functioning and most of them arise from gonadotrope cells and may secrete α and β-glycoprotein subunits.
- Hormone production does not always correlate with tumor size.

Classification of Pituitary Adenomas

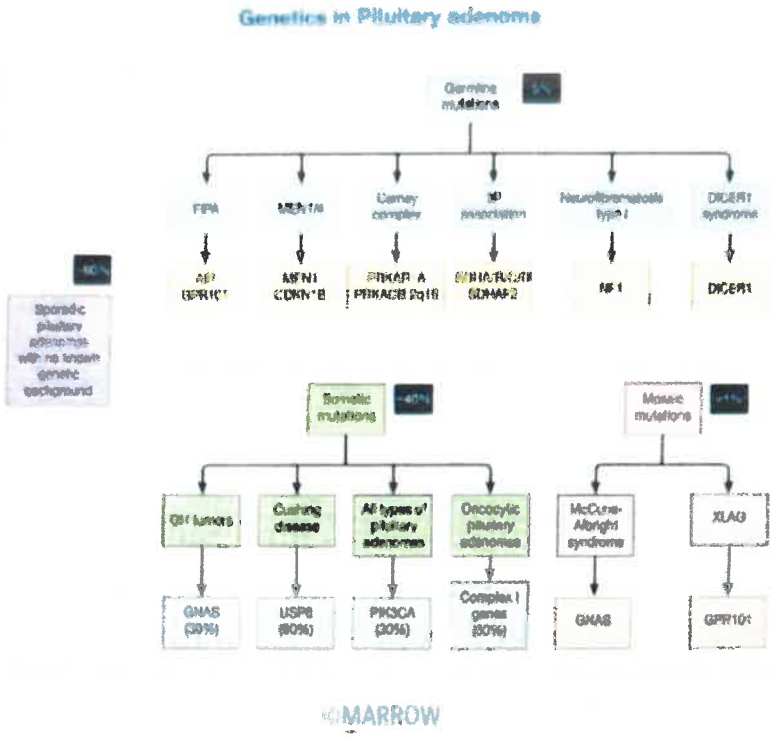
ADENOMA CELL ORIGIN	HORMONE PRODUCT	CLINICAL SYNDROME
Lactotrope	PRL	Hypogonadism, galactorrhea
Gonadotrope	FSH, LH, subunits	Silent, ovarian hyperstimulation, hypogonadism
Somatotrope	GH	Acromegaly/gigantism
Corticotrope	ACTH/none	Cushing's disease or silent
Mixed growth hormone and prolactin cell	GH, PRL	Acromegaly, hypogonadism, galactorrhea
Other plurihormonal cell	Any	Mixed
Acidophil stem cell	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Mammosomatotrope	PRL, GH	Hypogonadism, galactorrhea, acromegaly
Thyrotrope	TSH	Thyrotoxicosis
Null cell	None	Hypopituitarism/none
Oncocytoma	None	Hypopituitarism/none

Note :

- Silent adenomas : Immunohistochemical evidence of hormone production without biochemical or clinical features.
- Null cell adenomas : Immunostain negatively for all trophic hormones in addition.
- Crooke cell adenomas : massive accumulation of perinuclear cytokeratin filaments in response to glucocorticoid excess as seen in Cushing disease.

Genetics :

- No direct evidence in humans that pituitary hyperplasia is a prerequisite for tumor development.
- Tumors do not arise because of excessive polyclonal pituitary cell proliferation due to generalized hypothalamic stimulation.
- However, hypothalamic factors may promote and maintain growth of already transformed adenomatous pituitary cell.
- mostly are monoclonal in origin.
- Somatic mutations :
  - GSα mutations → Intrinsic GTPase activity → Cyclic AMP, Pit-1 induction, and activation of cyclic AMP response element binding protein (CREB) → Somatotrope cell proliferation and GH secretion.
  - 35% of GH-secreting pituitary tumors have sporadic mutations in GSα.
- Growth factors :
  - Pituitary tumor proliferation.
  - Basic fibroblast growth factor (bFGF) → Pituitary cell mitogenesis.
  - Epidermal growth factor receptor (EGFR) signaling induces hormone synthesis + cell proliferation
  - Mutations of USP8 may result in overexpressed EGFR in a subset of ACTH-secreting tumors.
- Oncogenes :
  - RAS and pituitary tumor transforming gene (PTTG).
  - Inactivation of growth suppressor genes : MEG3.
  - PTTG induces fibroblast growth factor (FGF) → Angiogenesis → Lead to dysregulated chromatid separation and cell aneuploidy.
- Cyclin-dependent kinase (CDK) complexes :
  - Lead to pRB phosphorylation, releasing E2F to promote cell cycle progression.
  - Cyclin D(CCND1) : Invasive, non-functioning pituitary adenomas.
  - Erb82 and Erb83 : Aggressive, recurrent prolactinomas.



Familial Pituitary Tumor Syndromes		
Syndrome	**GENE MUTATED**	**CLINICAL FEATURES**
Multiple endocrine neoplasia 1 (MEN 1)	MEN1 (11q13)	Hyperparathyroidism Pancreatic neuroendocrine tumors Foregut carcinoids Adrenal adenomas Skin lesions Pituitary adenomas (40%)
Multiple endocrine neoplasia 4 (MEN 4)	CDKN1B (12p13)	Hyperparathyroidism Pituitary adenomas Other tumors
Carney complex	PRKAR1A (17q23-24)	Pituitary hyperplasia and adenomas (10%) Atrial myxomas Schwannomas Adrenal hyperplasia Lentigines
Familial pituitary adenomas	AIP (11q13.2)	Acromegaly/gigantism (~15% of afflicted families)

McCune Albright syndrome :

- Polyostotic fibrous dysplasia, cafe au lait spots, acromegaly, adrenal adenomas.
- Gsα mutations causes this and occurs postzygotically.
- It is a non hereditary mutation.

Malignant pituitary tumors :

- No cell markers clearly distinguish aggressive invasiveness from malignancy.
- Demonstration of extracranial metastasis is a pre-requisite for diagnosis of pituitary malignancy.
- Temozolomide (Alkylating agent) :
  - To treat aggressive pituitary tumors.
  - O6-methylguanine DNA methyltransferase (MGMT) may interfere with drug efficacy.

Hyperprolactinemia /Prolactinoma 00:14:55

Prolactin (PRL) :

- 199 amino acids (GH has 194 AA).
- Secreted by lactotrophs (Acidophils).
- Act through JAK STAT Pathway.
- Mostly under inhibitory effect of dopamine (PIF).
- Present in CNS/placenta/uterus.
- Estrogen, TRH, VIP, oxytocin, REM sleep stimulates prolactin.
- M/C pituitary hormone hypersecretion syndrome in both men and women.
- Prevalence of 10/100,000 in men and 30/100,000 in women.
- Usually PRL levels >200 microgram/L.
- They are mixed tumors that secrete combinations of GH and PRL, ACTH and PRL, and rarely TSH and PRL.
- Microadenomas <1 cm; Macroadenomas are >1 cm.
- Giant prolactinomas : Defined as >4 cm in diameter and/or those with >2 cm of suprasellar extension.

Pathology and pathogenesis :

- 99% of prolactinomas are not malignant.
- Invasive tumors that do not metastasize are considered benign.
- Mostly slow growing, arise sporadically, usually occur singly.
- Pseudocapsule composed of compressed adenohypophyseal cells and a reticulin fiber network is seen.
- Female to male ratio for microprolactinomas is 20 : 1 and 1 : 1 for macroadenomas.
- 5% of microadenomas progress in the long term to macroadenomas.