Chapter

Pituitary Tumours

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Abstract

The chapter focuses on understanding the latest classification of the pituitary adenomas in light of immuno-histological and molecular signatures as envisaged in the latest WHO classification guidelines. It further looks into evaluating and analysing the symptoms of the adenoma locally and at distant organs. Imaging and hormonal analysis has been discussed in detail for both functional, non-functional and pituitary apoplexy. Further, the therapeutic options- medical, surgical and their outcomes have been highlighted.

Keywords: Functional, non-functional, recurrent, approach, outcomes

1. Introduction

Pituitary adenoma (PA) is the third most common intracranial neoplasm accounting for approximately 15% of all such tumors and is the commonest one, accounting for 85% of sellar and suprasellar region. These tumors arise from various cells in the pea sized gland, measuring about 0.5 gms, located in a bony cavity of the sphenoid bone called sella turcica (Latin for *Turkish seat*) covered by dura all around, cavernous sinuses laterally and its anterior and posterior intercavernous venous channels [1–4].

2. Development and histology

Human pituitary gland is composed of two anatomically and functionally distinct parts: the adenohypophysis (anterior) and the neurohypophysis (posterior). The adenohypophysis develops from an evagination of primitive stomatal ectoderm, Rathke's pouch. The neurohypophysis originates from the infundibular process of the diencephalon [5].

Adenohypophysis is an epithelial gland of endodermal origin and is composed of acini that contain the six specialized hormone- secreting cells within a reticulin -rich stroma. It is controlled by hypothalamic hormones that stimulate or inhibit the release of anterior pituitary hormones. The posterior pituitary is composed of axonal processes of neurons whose cell bodies are located in the supraoptic and paraventricular nuclei of the hypothalamus, and pituicytes (modified glial cells).

Pituitary development is complex and includes a highly spatio-temporally regulated network of integrating extrinsic signaling pathways and homeobox transcriptional factors. Timely activation of signaling molecules is required for

evolution of pituitary gland and to determine cell-specific lineages for hormone production [6].

The factors involved in early organogenesis and maintenance of pituitary primordium are six homeodomain proteins- (1) paired homeodomain proteins like *Prx 1* and *Prx 2*, (2) LIM homeodomain transcription proteins, (3) SOX transcription factors (4) WNT/ beta-catenin and (5) Notch signaling. Transcriptional factors which play main role in lineage determination, cytodifferentiation and hormonal production, that target specific hormonal genes.

3. Pituitary specific transcription factors

Three main pathways have been described in cell differentiation in adenohypophysis (**Figure 1**) and have become a part of tumour classification in the most recent WHO 2017 classification [7–9]:

1. Pituitary transcription factor 1 (PIT1): has role in differentiation of somatotroph, thyrotroph, lactotroph, mammosomatotrophs and their respective tumours.

2. Steroidogenic factor 1 (SF1): is responsible for differentiation of gonadotrophs and is expressed in gonadotrophic adenomas.

3. T-box pituitary transcription factor (TPIT): is responsible for transcription of pro-opiomelanocortin, a precursor of adrenocorticotrophic hormone and is expressed in corticotroph adenomas.

4. Ancillary IHC markers

1. Low molecular weight cytokeratin (LMWCK): are important in differentiating sparsely vs. densely granulated tumours. In the former, >70% of tumour is occupied with paranuclear cytokeratin positive fibrous body and less of secretory granules.

2. Estrogen receptor alpha (ER): is expressed in lactotroph and gonadotroph adenomas

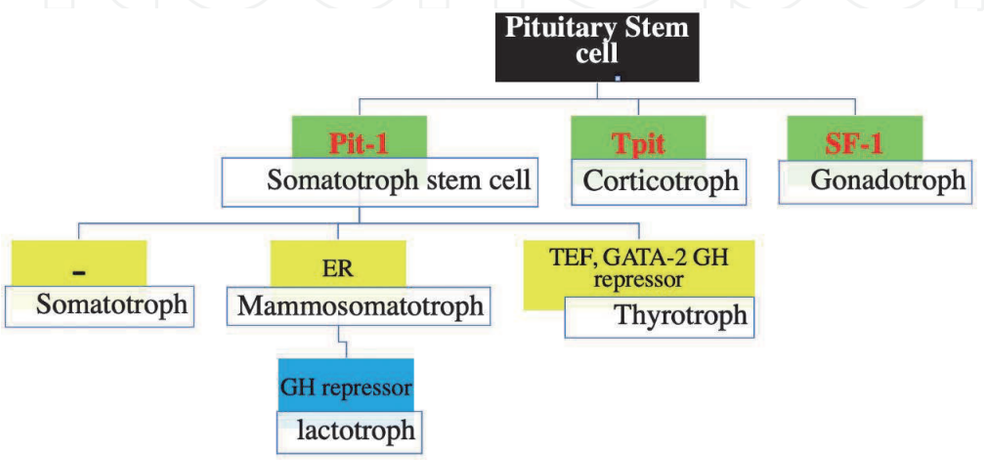

Figure 1.
Factors involved in lineage specific adenohypophysial cells.

3. GATA transcription factor 2 (GATA2): is expressed in gonadotroph and thyrotroph adenomas.

5. Genes associated with pituitary adenomas

Few genes have been identified as causes of pituitary adenomas-

5.1 Familial pituitary tumor syndromes

1. Multiple endocrine neoplasia type 1 (MEN 1)- Mutations in the coding for *menin*, reverses functions of tumor suppressor genes. Patients with MEN1 present with anterior pituitary adenomas in approximately 40% of all cases and have been described in children as young as 5 years. Most of the PAs in MEN1 are PRL-secreting (42–62%) or non-functioning tumors (15–42%), but GH- (6.5–9%) and ACTH-secreting (3–4%) adenomas have also been described. PAs in MEN1 have higher chance of co-secreting multiple hormones compared to *MEN1*-negative patients, in up to 39% of cases. PAs in MEN1 are considered more aggressive and at higher risk for resistance to treatment, especially in children with large prolactinomas [10–12].

2. Multiple endocrine neoplasia Type 2 (MEN-2)- are caused by *RET* gene mutations, which codes for a transmembrane receptor with tyrosine kinase activity acting as a proto-oncogene [12–15].

3. Multiple endocrine neoplasia type 4 (MEN 4)- is caused by *CDKN1B* gene mutations, which codes for a cyclin-dependent kinase (p27) that regulates cell cycle and progression from G1 to S phase of mitosis. MEN4 is a rare genetic syndrome, accounting for approximately 1.5–3% of patients clinically classified as MEN1, without genetic defects in *MEN1* gene [16–19].

4. Carney complex (CNC)- Carney complex (CNC) describes the constellation of myxomas, spotty skin pigmentation, and endocrine overactivity due to germline mutations of the *PRKAR1A* gene and are responsible for more than 70% of cases of CNC. *PRKAR1A* codes for the type 1 alpha regulatory subunit of the protein kinase A (PKA) tetramer, inactivation of which leads to dissociation of the regulatory from the catalytic subunit, aberrant activity of PKA and phosphorylation of downstream targets, leading to cell proliferation and tumour formation. Pituitary involvement in CNC is thought to be a progressive disorder with normal pituitary tissue progressing to somato-mammotroph hyperplasia and subsequently, to distinct tumour formation. Thus, multiple adenomas may be present synchronous or metachronous in the same patient [20–23].

5. Familial isolated pituitary adenomas (FIPA)- Familial pituitary tumors that are not associated with MEN 1 and CNC have been united under a new term-FIPA. It is used to describe families with at least two members with pituitary adenomas, with or without other abnormalities. About 15–25% of patients with FIPA harbour mutations in the AIP gene. This reaches up to 75% when families of GH-secreting adenomas are selected. AIP (aryl hydrocarbon receptor- interacting protein, 11q13) acts as tumor suppressor gene and its mutation predisposes to growth hormone secreting adenomas [24–27].

5.2 Sporadic pituitary adenomas

These account for 40% of GH adenomas and are due to mutations in Gs alpha gene mutations which results in cAMP/PKA signal transduction pathway leading to neoplastic transformation of somatotroph cells [28].

6. Pathology

All somatotrophic adenomas definitely express PIT-1 transcriptional factor and GH hormone. These tumors are broadly classified into pure somatotroph adenoma and Mixed somatotroph adenoma with co-expressing PRL or other hormonal markers. Based on secretary granules of GH, Pure somatotroph adenomas are further divided into two clinically significant and morphologically distinct subtypes: sparsely granulated (SG) and densely granulated (DG) somatotroph adenomas. Mixed SA are further classified into Mammosomatotroph adenomas (MSA), mixed somatotroph-lactotroph adenomas (MSLA) and plurihormonal adenomas.

Similar to other adenomas, SA are soft white to grey macroscopically. MSA are smaller in size with better prognosis compared to MSLA are larger with more invasiveness at the time of presentation.(75) SA are often seen arising from GH expressing pituitary cells in lateral wing of the gland. Extra seller extension of these tumors gives a characteristic shape of snowman (76).

Microscopically, SA share characteristics of other endocrine tumors: colonies of relatively large monomorphic cells with eosinophilic cytoplasm and spherical nuclei. Disruption of dense reticulin meshwork around the nests of cells distinguishes PA from normal pituitary cells (**Figure 2**). Hyperplasia to adenoma progression of SA were observed in some cases with familial isolated pituitary adenoma and X-linked acro-gigantism syndrome. (112) DGSAs are the most common and expresses diffuse cytosolic positively of GH and cytokeratin (CAM 5.2). These are predominantly seen in older age group with slower growth and excellent response to somatostatin treatment. SGSA are less common and behave differently with more aggressive nature like being larger, more invasiveness & proliferation and poor response to somatostatin response. They show co-segregation of cytokeratin and growth hormone granules resulting in characteristic fibrous bodies. These bodies are juxtanuclear keratin aggregates highlighted by cytokeratin immunohistochemical stain (CAM 5.2). MSA are histologically similar to DGSA and ultra-structurally distinct a single cell expressing both GH and PRL granules. MSLA are composed of

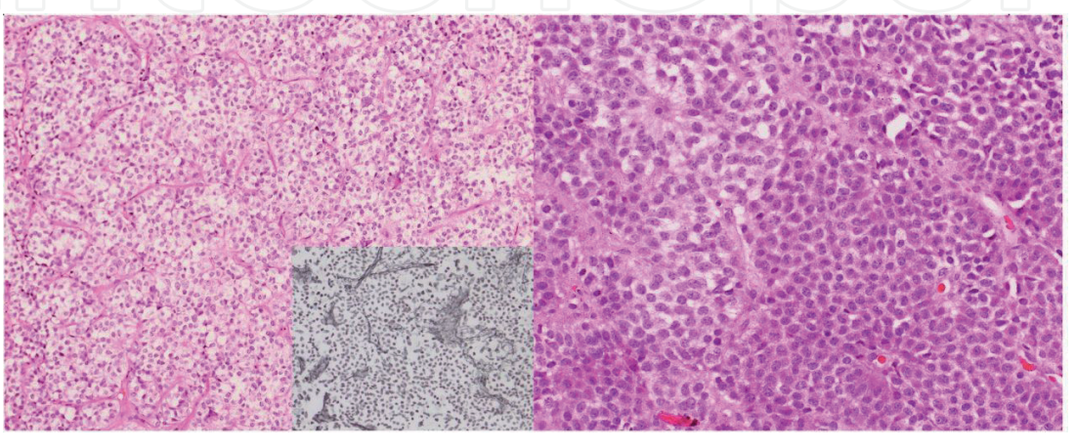

Figure 2.
Histopathological section of pituitary adenoma exhibit colonies of monomorphic round cells with disruption of reticulin meshwork. (H & E 100X, (insert- Reticulin stain) and 200X).

mixture of two different cells with GH and PRL secreting granules respectively. Either of the cell population can be densely or sparsely granulated with various combinations.

7. Radiology of pituitary tumors

'The Pituitary Body and its Disorders' was one of the first books written on the subject of Neuroradiology, based on work done at the Johns Hopkins Hospital, and consisted of detailed explanation of lesions detected on radiographs [29].

Pituitary imaging is indicated in patients, presenting with symptoms secondary to derailed pituitary hormones or symptoms indicating pituitary mass, like visual field deficit or headaches.

The sella turcica, as described earlier in chapter, is located deep within the cranium and can be demonstrated on a number of projections of skull radiographs. A right or left true lateral view of the skull demonstrates a clear profile view of sella and dorsum sellae. In a properly positioned lateral skull supine view, the line extending from the outer canthus of the eye to the external auditory meatus is perpendicular to the table. A caudally angled occipito-frontal projection, or Skull PA Axial (Caldwell View) is taken to demonstrate the floor of sella turcica. In this view, X-rays pass at an angle of 15 degrees from occiput and exit at the nasion, with film kept perpendicular to the orbitomeatal line (OML). For demonstration of dorsum sellae through the foramen magnum, Haas View, another Skull PA Axial view is taken where the central ray is angled 25 degrees cephalad to the orbitomeatal line (OML). The patient sits or stands facing an upright Bucky with the forehead and nose touching the imaging receptor. The neck is flexed to bring the OML perpendicular to the IR. It has been proven that PA axial radiographs add wealth of information pertaining to sella, and is complimentary to the sagittal view [30, 31].

Radiographic signs associated with pathology of pituitary gland and surrounding structures include i) enlargement with associated distortion of shape of the sella turcica, usually associated with empty sella syndrome or pituitary tumors, ii) Erosions in the floor or lateral walls, secondary to aneurysms or chronic increased intracranial pressure, iii) Sclerosis of the tuberculum or clinoid processes due to meningioma involving diaphragm sellae, iv) Sclerosis of sellar floor likely secondary to nasopharyngeal carcinoma or craniopharyngioma, v) Fat or calcifications in the intrasellar, suprasellar or parasellar region indicate presence of germ cell tumors or craniopharyngioma, vi) Eggshell calcification may point towards presence of aneurysms, Rathke's cyst or craniopharyngioma [32–34]. Usually sellar to cranial index of more than 8 is considered as abnormal and indicative of a sellar lesion on lateral skull radiograph [35].

With advent of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI), MRI has become the modality of choice for imaging of pituitary lesions, due to its better soft-tissue contrast details and its ability to demonstrate pituitary gland and parasellar anatomy with increased spatial resolution and without artefacts from surrounding bones. CT is usually reserved for patients with contraindications to MRI and for those undergoing emergent evaluation.

In normal adults, the anterior pituitary is isointense to grey matter on T1-weighted and T2- weighted sequences, while posterior pituitary is inherently hyperintense onT1 weighted sequences, appearing as bright spot, secondary to antidiuretic hormone neurosecretory granules present within the posterior pituitary. In neonates till 2 months of age and in pregnant women, the anterior pituitary may be as hyperintense as the posterior pituitary. On post contrast dynamic

imaging, the enhancement of infundibulum is seen earlier than posterior pituitary, which turn enhances earlier than anterior pituitary [36].

Radiologically, pituitary adenomas are classified by size; microadenomas are 10 mm or less in diameter, and macroadenomas are greater than 10 mm in diameter. Microadenomas usually show signs and symptoms of hormonal excess, and if suspected, previous biochemical analysis for pituitary hormones is helpful in indicating a dynamic pituitary scan for their diagnosis. They could be either, prolactinomas, growth hormone-secreting adenomas or ACTH-secreting tumours. On MRI, microadenomas are iso to hypointense on T1W images and usually appear hyperintense on T2W sequences. Dynamic imaging following bolus injection of contrast, is helpful in depicting differential uptake of contrast between a microadenoma and normal pituitary gland and thus increases the detection rate of microadenomas [37, 38].

Pituitary macroadenomas are twice as common as microadenomas and are the most common suprasellar masses, resulting in visual symptoms. A slow-growing macroadenoma expands the bony sella and extends into the suprasellar cistern, giving "figure of 8" or "snowman" like appearance because the rigid diaphragm sellae. On CT imaging, macroadenomas are isodense to the surrounding brain, however, scalloping/destruction of the surrounding bones is better depicted on CT. On MRI, macroadenoma appears isointense to gray matter on T1- and T2-weighted MR images, and usually demonstrates intense contrast enhancement unless there are areas of necrotic degeneration or hemorrhagic foci within [39].

Invasive macroadenomas are usually prolactin-excreting tumors, and in such cases prolactin levels found are more than 1000 ng/dL [40]. It is difficult to distinguish invasive adenomas from rarer pituitary carcinoma, only on imaging.

Microadenomas may occasionally present with intrapituitary hemorrhage or tumor cyst without discerning solid component on MRI. Such cystic lesions within microadenomas are usually off midline unlike Rathke's cleft cyst, and are sometimes difficult to differentiate. In such cases, temporal growth of the lesion or associated hormonal changes give an indication of tumoral lesion. Intralesional hemorrhage can be picked up as hyperdense focus on CT and show peculiar MRI signal on T1W and T2W sequences based on the age of bleed.

Non adenomatous tumors of pituitary like, pituicytoma, spindle cell oncocytoma or granular cell tumors, are usually suprasellar/infudibular in location and some of them like granular cell tumors appear hyperdense on CT. Pituicytomas show homogeneous vascular enhancement on post contrast studies and are more vascular than adenomas, and their posterior location and increased vascularity makes them amenable for complete resection [41].

8. Classifications

Pituitary adenomas are broadly classified as functioning or non-functioning adenomas based on hypersecretion of specific hormones [42–47].

Functioning adenoma account for 2/3 of pituitary adenomas and present with specific clinical sign and symptoms related to excess hormonal secretion. Non-functioning adenomas account for 1/3 of all pituitary tumors, where they present incidentally or with clinical signs and symptoms related to degree of mass effect on adjacent structures with no evidence of hormone excess either clinically or on biochemical analysis. These are considered to be producing inactive peptides/glycoproteins or the hormone secretion was defective. These are further subtyped as-silent adenomas and null cell adenomas.

The definitions and thus the incidence of such adenomas has seen a sea of change with the addition of transcription factors and other IHC markers. Null cell

adenomas are defined as non-functional adenomas that are immune-negative for all hormones and pituitary specific transcription factors and has led to decrease of their incidence from 16.5% to <1% and has also led to the emergence of silent gonadotroph adenomas which were underdiagnosed. Silent adenomas were earlier described on ultrastructural findings on electron microscopy are now defined as tumors with no clinical or biochemical features of hormone excess but are positive for pituitary specific transcription factors. Silent corticotroph adenoma was classically described and subtyped as- I) densely granulated, II) sparsely granulated and III) Subtype 3. The immunoreactivity with PIT1 and inconsistent immunoreactivity to POMC has led to dropping of the word "corticotroph" from subtype 3and has been classified along with plurihormonal PIT1 adenomas (**Table 1**).

The new WHO classification of tumors of pituitary was mainly based on morphology and function of tumor cells (**Table 2**). Diagnostic and prognostic practical aspects included in new WHO are summarized below:

1. Elimination of term 'Atypical Adenoma': This term atypical adenoma was used for invasive tumors with invasiveness with elevated Ki67/MIB-1 and > 3% immunostaining for p53. This has been replaced by "high risk adenomas" and Includes

    a. Sparsely granulated somatotroph adenoma

    b. Lactotroph adenoma in men

    c. Crooke's cell adenoma

    d. Silent corticotroph adenoma

    e. Plurihormonal PIT1 positive adenoma.

2. Deletion of the term Oncocytoma, which is now considered a subset of gonadotroph adenoma.

3. A novel approach for classifying pituitary neuroendocrine tumors according to pituitary adenohypophyseal cell lineage pituitary specific transcription factors.

4. Re-definition of old entities like the null-cell adenoma based on pituitary specific transcription factors.

5. Introduction of new entities like pituitary blastoma, associated with DICER1 mutations, occurring exclusively in infants and children younger than 24 months.

Transcription factors	IHC	Diagnosis
SF1 +	FSH+/LH+/ER+	Gonadotroph
SF1 +	FSH-/LH−/ER-	Gonadotroph
TPIT1+	ACTH-	Silent corticotroph
TPIT 1+	ACTH +	Silent corticotroph
PIT 1+	Variable GH/Prl/TSH/ER	Pit-1 lineage, poorly differentiated
PIT 1+	LMWCK+, Variable GH/Prl/TSH/ER	Silent subtype 3

Table 1.
Clinically non-functional adenomas.

S.No	Adenoma type	Morphological subtypes	Hormonal markers	Transcriptional factors	Cytokeratin (LMWCK)	Prognosis
1	Somatotroph adenoid	Densely granulated somatotroph adenoma	GH ± PRL ± α-subunit	PIT-1	Perinuclear or diffuse positivity	
		Sparsely granulated somatotroph adenoma	GH ± PRL	PIT-1	Dot-like (fibrous body)	Aggressive
		Mammosomatotroph adenoma	GH ± PRL ± α-subunit	PIT-1, ER-∝	—	
		Mixed somatotroph-lactotroph adenoma	GH ± PRL (in different cells) ± α-subunit	PIT-1, ER-∝	—	
2	Lactotroph adenoid	Densely granulated lactotroph adenoma	PRL	PIT-1, ER-∝	—	
		Sparsely granulated lactotroph adenoma	PRL	PIT-1, ER-∝	—	
		Acidophil stem cell adenoma	PRL ± GH,	PIT-1, ER-∝	Dot-like (fibrous body)	Aggressive LA in men show aggressive behaviour
3	Thyrotroph adenoid		b-TSH, α-subunit	PIT-1, GATA2	—	
4	Corticotroph adenoid	Densely granulated	ACTH,	T-PIT	Diffuse	
		Sparsely granulated	ACTH,	T-PIT	Diffuse	
		Crooke's cell adenoma	ACTH,	T-PIT	Ring-like	Aggressive Silent CA show aggressive behavior
5	Gonadotroph adenoid		b-FSH, b-LH, α-subunit	SF-1, GATA2, ER-∝	—	
6	Null cell adenoid		No markers	None	—	
7	Plurihormonal adenoid	Plurihormonal PIT-1 positive adenoma (previously called subtype 3 adenoma)	GH, PRL, b-TSH, ± α-subunit	PIT-1	—	Aggressive
		Adenoma with unusual immunohistochemical combination	various		—	

Table 2.
Classification of Pituitary Adenoma. Modified from the 2017 WHO classification of tumors of pituitary gland.

6. Introduction of new entities like plurihormonal tumors based on immunohistochemical combinations.

7. Introduction of double/multiple adenomas that show geographically distinct cell populations.

8. Replacing terminologies like term "hormone producing" has been changed to 'troph' to emphasize the role of transcription factors in cell differentiation and specific regulatory hormones of adenohypophysis.

Significant changes affecting the diagnosis of pituitary adenomas (PA) were introduced, and simultaneously panels of experts have also proposed replacing the term PA for Pituitary neuroendocrine tumour (Pit NET) [42–47].

9. Non-functioning pituitary adenomas

Non-functioning pituitary adenomas (NFPAs) are benign pituitary neoplasms that arise from the adenohypophyseal cells and lack clinical or biochemical evidence of hormone excess except for a mild hyperprolactinaemia in some cases, due to stalk effect. They account for 14–54% of pituitary adenomas. These include the silent adenomas and the null cell adenomas. Oncocytomas, which were included as a subset of null cell adenomas are now an obsolete term, and are accepted as phenotype with abundant mitochondria.

Immunohistochemical, secretory studies, in vitro tissue cultures have demonstrated the presence of all adenohypophyseal hormone components in the adenomas, the most common being the gonadotrophs. Even electron microscopic studies have shown that these tumour cells have secretory granules despite having assayable hormones. Chromophobe adenomas have also shown staining for ACTH despite being clinically negative for Cushing's syndrome or elevated cortisol levels.

9.1 What makes these tumors non-functional?

Various explanations have been offered to these tumours which have positive transcription factors except null cell adenomas for being hormonally or clinically negative. These are-

1. The glycoprotein hormones like FSH, LH, TSH need a combination of both alpha and beta subunits and these tumours might be producing the uncombined subunits and hence are clinically inactive.

2. Low levels of hormone production resulting in near normal values.

3. Abnormalities is secretion despite normal synthesis.

4. Lack of specific assays for subunit detection [48–52].

9.2 Clinical presentation

The clinical spectrum of NFPA varies from being completely asymptomatic to causing significant hypothalamic/ pituitary dysfunction and visual field compromise due to their large size. The absence of clinical symptoms of hormonal hypersecretion causes a delay in diagnosis with a mean time of delay

1.96 ± 2.9 years. Most patients present with symptoms of mass effect, such as headaches, visual field defects, ophthalmoplegias, and hypopituitarism. Other manifestations are hyperprolactinaemia due to pituitary stalk deviation and less frequently pituitary apoplexy (3.7–14.1%) [53, 54].

Headaches have been described with a varying incidence of 19–75% regardless of the size of the tumours. The possible reasons for the headaches are- (a) increased intrasellar pressure and stretching of dural membranes containing pain receptors, (b) activation of trigeminal pain pathways by tumours affecting the cavernous sinus (c) due to apoplexy, or (d) hydrocephalus [55].

Neuroophthalmological symptoms are caused by the pressure effects, ischemia or a combination of both on the on the optic chiasm. The typical visual field defect associated with pituitary tumours is bitemporal hemianopia, occurring when the body of the chiasm (which is comprised of the crossing nasal fibres of each optic nerve) is compressed by the enlarged gland. Variations in the anatomy of the chiasm leads to different patterns of field loss which can be uni-, bilateral or even central. The defect may be complete, involving the whole hemi-field or partial, usually beginning superiorly and progressing inferiorly, depending on the degree of nerve compression. Macular fibres, located in the postero-superior quadrant are more distant and are late to be involved. Chronic compression may lead to primary optic atrophy and may lead to decrease in the visual acuity.

Ophthalmoplegia is caused by pressure on the abducens or oculomotor nerves in the cavernous sinus. The invasion of the cavernous sinus (parasellar expansion) may affect the cranial nerves, causing a varied clinical profile according to the compromised nerve: ptosis (III nerve lesion), deviation of the eyeball superiorly and slightly inward (IV nerve involvement) and convergent strabismus (lesion VI nerve) [56].

Giant tumours, defined as ≥40 mm in one dimension or within 6 mm of Foramen of Monro, may rarely cause obstructive hydrocephalus. Erosion of the sellar floor may lead to CSF rhinorrhoea [57–59].

NFPAs may demonstrate mild elevations in serum prolactin ("disconnection hyperprolactinaemia"), due to blockage of dopamine which inhibits the lactotrophs. However, this value is never beyond 2000 mU/L. Mechanical compression of the normal anterior pituitary gland and/or pituitary stalk may prevent the passage of stimulatory hypothalamic factors resulting partial or complete hypopituitarism. Hypopituitarism develops slowly and often goes undetected. The overall prevalence of partial hypopituitarism in patients with NFPAs ranges from 37 to 85%. Panhypopituitarism occurs in 6–29% of patients and GH axis is affected in 61–100% of patients showing laboratory evidence of GH deficiency [60–62].

Central hypogonadism is noted in 36–96% of patients and adrenal insufficiency is noted in 17–62%. Finally, 8–81% exhibit central hypothyroidism. Presentation with diabetes insipidus is very rare [63].

9.3 Investigations

The investigations are aimed at-

1. Detecting the hormonal deficiencies,

2. Find out any hormonal excess especially double dilution to rule out Hook effect in hyperprolactinemia.

3. Imaging, the preferred one is MRI brain to demonstrate the morphology of the tumor, invasion of surrounding structures and assess the targeting routes.

4. Neuro-opthmological evaluation includes visual acuity, field vision and fundus characterisation.

The differential diagnosis of an incidentally discovered sellar mass is broad and includes a large number of entities: anterior pituitary tumours, posterior pituitary tumours (e.g., pituicytoma, granular cell tumours), benign parasellar tumours (e.g., meningioma, craniopharyngioma), malignant tumours (e.g., glioma, germ cell tumour), developmental lesions (e.g.,, Rathke's cleft cysts, dermoid cyst, epidermoid cyst, arachnoid cyst), inflammatory and granulomatous lesions (e.g., lymphocytic hypophysitis, granulomatous hypophysitis, Langerhans cell histiocytosis) and vascular lesions (e.g., aneurysms) [62].

9.4 Grading of tumor

1. Based on the size of tumor

   a. Microadenomas- less than 10 mm

   b. Macroadenomas- 10 mm to 40 mm in size

   c. Giant pituitary adenomas- tumors in excess of 40 mm in size, or extending within 6 mm of Foramen of Monro

2. **Hardy's Classification** [64–66]

   The large variation in sellar invasion and suprasellar extension of pituitary adenomas was recognized in the 1970s by Hardy and Vezina and prompted the development of the Hardy classification criteria to better characterize these lesions. Since that time, the Hardy classification system has served as a descriptive tool for pituitary adenomas and is often utilized in research studies. The Hardy classification comprises of two subscales: one describes the integrity of the sellar floor and invasion into the sphenoid sinus (Grades 0–IV), whereas the other describes the degree of suprasellar extension of the tumor (Types A–D). Although these two subscales were described using lateral radiographs and encephalograms, respectively, the Hardy grading scale is still used to classify adenomas based on magnetic resonance imaging (MRI) scans.

Sellar Invasion	
Grade 0	The enclosed adenoma is described as a tumor that remains within the anatomical confines of the osteo-aponeural sheath of the sella turcica. The floor of the sella is always intact.
1	The sella turcica is within normal limits in size (less than 16 × 13mm; 208 mm) but shows a lowering of the floor on one side or a bulging of the cortex.
2	The sella turcica is enlarged to various degrees but the floor remains intact.
3	The sella is more or less enlarged but there is a local erosion or destruction of the floor.
4	The entire floor of the sella is diffusely eroded or destroyed, giving a characteristic "phantom sella" with all the boundaries barely visible.
Suprasellar extension	
Type O	The tumour is entirely confined within the sella turcica.
A	The suprasellar expansion bulges into the chiasmatic cistern but does not reach the floor of the anterior third ventricle.

B	The tumour reaches the floor of the third ventricle, giving the image of an inverse cupula of the anterior recesses of the third ventricle.
C	A voluminous suprasellar expansion bulges largely into the third ventricle up to the foramen of Monro.
D	Rare aberrant expansions occur in temporal or frontal fossa.

3. Wilson's modification of Hardy's classification [67]

Wilson modified Hardy's classification to distinguish between extrasellar extensions, including extension into the cavernous sinus.

Suprasellar extension

0: none
A: expanding into suprasellar cistern
B: anterior recesses of 3rd ventricle obliterated
C: floor of 3rd ventricle grossly displaced

Parasellar extension

D: intracranial (intradural); specify (1) anterior (2) middle, or (3) posterior fossa
E: into or beneath cavernous sinus (extradural)

Invasion

Floor of sella intact

I: sella normal or focally expanded; tumor <= 10 mm
II: sella enlarged; tumor > = 10 mm

Sphenoid extension

III: localized perforation of sellar floo
IV: diffuse destruction of sellar floor

Distant spread

V: spread via CSF or blood-borne

4. Knosp's grading for invasiveness into cavernous sinus

Knosp et al. introduced a classification of the parasellar extension of PAs based on MRI coronal sections. Three lines (medial, median and lateral), which cross the internal carotid artery (ICA), determine the degree of invasion. They further suggested a subdivision of grade 3 into 3A and 3B: in Grade 3A, the tumor extends laterally in the superior compartment of the cavernous sinus, whereas in Grade 3B the lesion extends laterally, but in the inferior compartment. This finding is clinically and biologically relevant, and is most probably the consequence of better surgical visualization provided by an endoscope [68–70].

Grade 0	No involvement of the cavernous sinus (normal condition)
1	The tumour pushes into the medial wall of the cavernous sinus, but does not go beyond a hypothetical line extending between the centres of the two segments of the internal carotid artery (non-invasive PA)
2	The tumour goes beyond hypothetical line, but without passing a line tangent to the lateral margins of the artery itself (non-invasive PA)

3	The tumour extends laterally to the internal carotid artery within the cavernous sinus (invasive PA)
4	Total encasement of the intra-cavernous carotid artery (invasive PA)

9.5 Treatment

The primary goal of treatment of these non-functioning adenomas is reduction of the tumour mass and relieve the compressive effects on the optic apparatus, ventricular system, cavernous sinus and adjacent brain parenchyma.

In the absence of visual impairment, the optimal treatment choice is still a matter of debate, especially in patients presenting with hypopituitarism, headache, or tumours close to the chiasma. Surgery may improve pituitary function in up to 30% of patients with pre-existing hypopituitarism, but the risk of new hormone deficiency following surgery is 2–15%. Therefore, hypopituitarism alone is not an indication for surgical treatment. Surgical resection of non-functioning microadenomas is not indicated since tumour growth is rare (3–13%) with less than 5% growing > 1 cm during long-term follow-up.

Surgical excision either through trans-sphenoidal endoscopic or microscopic or trans-cranial route are the mainstay.

Bromocriptine, Octreotide and other agents have been shown to be partially successful in reducing the tumour.

Radiotherapy is indicated in case of inadequate tumour resection, high mitotic index and at recurrence.

Gross total resection is achieved in 60–73% of patients with NFPAs. In a recent meta-analysis on NFPA patients, TSS was associated with 1% mortality. Postoperative complications such as cerebrospinal fluid (CSF) leakage, fistula, meningitis, vascular injury, persistent DI, or new visual field defect occurred in ≤ 5% of patients. Surgical complications are reported to be less frequent with higher-volume surgeons or hospitals. The risk of CSF leakage is increased in patients with large adenomas with suprasellar extension, intraoperative CSF leakage, repeat TSS, and high body mass index.

9.6 Outcomes

The visual improvement in acuity and visual fields is seen in 70–80% following gross total or subtotal excision of tumours [71–73].

9.7 Residual or recurrent NFPA

The rate of complete excision of these nonfunctional adenoma varies from 60 to 70% depending on the experience of surgeon. Additional use of intra-operative MRI has increased the rate of complete removal to 82%. Factors leading to less than complete removal are- 1) invasion into cavernous sinus, 2) increased diameter, and 3) absence of apoplexy [74].

Recurrences following complete removal of tumour is usually low. Recurrence rates in 10-year follow-up was found to be approximately 5%, 25% and 50% for initial complete removal, suspicious residue and initial incomplete removal, respectively.

Indications for re-surgery for both recurrences or growing remnants are- 1) increasing tumour size, 2) new endocrinological deficits and 3) new ophthalmological symptoms.

Management of recurrence is based on the following factors- 1) time of tumour recurrence, 2) size and location, 3) age, 4) general condition, 5) ophthalmological findings, 6) neurological findings and 7) endocrine findings.

Re-do surgery is recommended for accessible tumours in young and healthy adults. Early recurrences after complete excision are better treated with radiotherapy. Small and asymptomatic recurrences need to be followed up for tumour growth and clinical factors. Elderly with severe systemic diseases is managed conservatively [75–86].

10. Lactotroph adenomas or prolactinomas

LA are also derived from PIT-1 lineage adenohypophyseal cells with chief expression of PRL. LA are the most common hormone expressing pituitary adenoma, accounting for 30–50% of all adenomas. The reported prevalence is 35 per 100,000 people. The highest incidence is seen in women of child-bearing age and in patients with MEN 1 [87–90].

10.1 Clinical presentation

This endocrinopathy which was classically described as amenorrhea-galactorrhea syndrome was first described to be associated with prolactin hypersecretion by Forbes in 1954. However, the manifestations are quite varied among the genders and in females in relation to their menopausal status. The increased levels of prolactin cause decrease in the levels of gonadotropins resulting in hypogonadism. In females in reproductive ages, they present with- 1) delayed puberty, 2) oligomenorrhea, 3) primary or secondary amenorrhea or 4) regular menstural cycles with infertility. Galactorrhea is seen in 30–80% females in this age group. Post-menopausal women and men, who conspicuously lack these features, present with visual disturbances and subtle symptoms like loss of libido or dyspareunia. Osteoporosis which was earlier considered due to direct effects of prolactin on the bone is correlated to hypogonadism and lack of estrogen in women. Headaches are a common presentation in all. Psychiatric manifestations include hostility, depression, anxiety and weight gain [90–92].

10.2 Pathology

Macroscopically, LA are pseudo capsulated and show grey white appearance with firm consistency and gritty on cut. Stromal amyloid deposition and microcalcification are observed in few cases. Some tumors have microscopic invasion and some macroadenoma are widely invasive into adjacent structures. SGLA are distinct from DGLA, as the prolactin staining pattern is paranuclear golgi type. ASLA are composed of abundant vacuolated eosinophilic cytoplasm, so called oncocytic change and occasional fibrous bodies.

Immunohistologically, these tumors are subdivided into sparsely granulated lactotroph adenoma (SGLA), densely granulated lactotroph adenoma and acidophil stem cell adenoma (ASCA). These subtypes have a distinct biological behavior and response to treatment. LA are most common in women and predominantly seen in childhood and adolescents age group. Biological and prognostically distinct differences are observed between males and females. In men, tumor present more aggressively with invasiveness and 80% are larger of them are macroadenoma, whilst size of tumor is small in women. Estrogen plays a significant role in

pathogenesis of tumor. A significant correlation between the estrogen receptor and tumor volume was observed, but mechanism is not known.

10.3 Laboratory evaluation

The normal levels of prolactin are <20 ng/ml. Single elevation of >200 ng/ml are almost always due to prolactinomas. However, the values between 20 and 200 ng/ml need careful evaluation of drug, systemic condition and correlation with the size of the tumour to rule out "pseudo-prolactinomas" due to "stalk sectioning effects" [93].

Prolactin may be elevated in other conditions as well. Hence, a careful history especially pertaining to drugs needs to be taken (**Table 3**). Non–prolactin-producing macroadenomas can cause prolactin elevations from disinhibition of prolactin secretion by compressing the pituitary stalk or hypothalamus. Very high prolactin levels seen in macroadenomas can saturate the antibodies in the assays and lead to artifactually low or normal results (the "Hook effect") and prolactin levels should be rerun at 1:100 dilution to exclude this possibility [8].

Two distinct biological profiles of prolactinomas have been observed- 1) benign microadenomas with very little growth potential and 2) aggressive, invasive macroadenomas. Natural history and autopsy studies have shown that not all microadenomas proceed to develop into macroadenomas. The risk of progression of

Hypothalamic causes	Craniopharyngiomas Meningiomas Dysgerminomas Sarcoidosis Langerhans cell histiocytosis Vascular Pituitary stalk section
Pituitary causes	Prolactinomas Acromegaly Lymphocytic hypophysitis Cushing disease Non secreting adenomas (stalk compression)
Medications	Phenothiazines Haloperidol Atypical antipsychotics Monoamine-oxidase inhibitors Tricyclic antidepressants Reserpine Methyldopa Metoclopramide, Levosulpride Verapamil Serotonin reuptake inhibitors Estrogen
Neurogenic	Chest wall lesions Spinal cord lesions Nipple stimulation
Other	Pregnancy Hypothyroidism Chronic kidney disease Cirrhosis Pseudocyesis

Table 3.
Causes of hyperprolactinemia.

microadenomas to macroadenomas is 3–7%. However, the natural history of macroprolactinomas is not known. The risk of macroadenomas enlarging during pregnancy is approximately 15%.

Dopamine agonist therapy is the mainstay of treatment, instituted to lower prolactin levels, decrease tumour size, and restore gonadal function for patients harbouring symptomatic prolactin-secreting microadenomas or macroadenomas.

Bromocriptine, the prototype dopamine agonist was introduced into clinical trials in 1971. It acts by stimulating dopamine receptors on lactotrophs, a potent analogue of dopamine, decreases cAMP activity, reduction in intracellular calcium, and hence decreased synthesis and release of prolactin. It is given in doses of 5-20 mg/day in three divided doses. The cellular and ultra-structural changes noticed after bromocriptine therapy are- 1) loss of cytoplasmic volume, 2) involution of rough endoplasmic reticulum, 3) at subcellular level, decrease in prolactin gene transcription and translation, 4) in vivo PET studies demonstrating reduced metabolic activity and 5) varying degrees of calcification, amyloid deposition, perivascular and interstitial fibrosis. All the above except 5, are reversible especially in macroadenoma. The fibrosis may preclude successful tumour excision. Bromocriptine resistance may be noted in 25% patients, 80% of whom may show response to cabergoline [94, 95].

The long-acting dopamine agonist cabergoline is preferred due to its higher efficacy in normalizing prolactin levels and pituitary adenoma shrinkage [8]. The higher efficacy is probably due to the higher affinity for dopamine receptor binding sites. Control of hyperprolactinemia requires doses of cabergoline ranging from 0.25 to 3 mg/wk.; resistance to cabergoline may be seen in upto 10% patients and may require doses up to 11 mg/wk. [12, 13]. Echocardiograms should be advised yearly in those patients exceeding a weekly dose of 2 mg, to look for valvular regurgitation [96].

Another adverse effect of dopamine agonist, occurring in about 5% of patients, is compulsive behaviour, such as excessive gambling and hypersexuality. Asymptomatic patients harbouring a microprolactinoma may be followed up without treatment. In patients with amenorrhea due to the microadenoma, the clinician can choose between a dopamine agonist or oral contraceptives.

Resistance to therapy is defined by failure to achieve a normal prolactin level and failure to achieve a 50% tumour reduction after maximal conventional doses of DA (Bromocriptine >15 mgs per day or 2 mg/week of cabergoline for at least 3 months). The possible reason for resistance is decreased D2 receptor expression or mutations in post receptor mechanisms.

The alkylating agent, Temozolamide, has been used in patients with malignant prolactinomas.

Patients on medical management should be followed up at regular intervals in the following manner:

a. Serum prolactin levels to be measured at regular intervals, beginning 1 month after the start of treatment in order to guide the clinician for titration of dopamine agonist therapy to achieve normo-prolactinemia/restore eugonadal status.

b. Repeat MRI in 1 yr.

c. Earlier repeat MRI (in 3 months) in patients with macroprolactinoma, if prolactin levels continue to rise while patient is receiving dopaminergic agents, or in the presence of new symptoms, e.g., galactorrhoea, visual disturbances, headaches, or other hormonal disorders.

d. Visual field examinations in patients with macroadenomas at risk of impinging the optic chiasm

e. Evaluation and management of comorbidities, e.g., sex steroid-dependent bone loss, persistent galactorrhoea and pituitary trophic hormone reserve.

10.4 Surgical Indications for prolactinomas

1. Pituitary Apoplexy
2. Visual deficits due to compression of the optic apparatus
3. Cystic prolactinomas
4. DARP- Dopamine agonist resistant prolactinomas
5. Women seeking fertility
6. CSF fistulas
7. Recurrent tumors
8. Increasing tumor during pregnancy
9. Macroadenoma in psychiatric patients

Remission rates after surgical excision vary from 30 to 93%. Restarting DA following surgical decompression normalises prolactin levels which can be maintained at lower doses [97–101].

10.5 Surgical issues with pregnancy in prolactinomas

The major issue with regards to pregnancy in patients with prolactinomas are

1. Infertility
2. Risk of tumour growth during pregnancy
3. Effects on foetal growth

The risk tumour enlargement is upto 5% for microadenomas while it reaches upto 15% for macroadenomas. However, prior surgery and/or radiotherapy reduces this risk to 4.3%. Both surgery and bromocriptine therapy are equally effective in microadenomas for fertility. However, no such comparison is available for macroadenomas. Bromocriptine needs to be stopped at the first sign of pregnancy [100, 102].

11. Somatotroph adenoma

Somatotroph adenoma (SA) is a subtype of pituitary adenoma which are derived from PIT-1 lineage cells with GH expression and with or without co-expression of prolactin (PRL). These tumors account for 10–15% of all pituitary adenoma, and can occur at any age with mean age at diagnosis of 47 years.

11.1 Pathology

All somatotrophic adenomas definitely express PIT-1 transcriptional factor and GH hormone. These tumors are broadly classified into pure somatotroph adenoma and Mixed somatotroph adenoma with co-expressing PRL or other hormonal markers. Based on secretary granules of GH, Pure somatotroph adenomas are further divided into two clinically significant and morphologically distinct subtypes: sparsely granulated (SG) and densely granulated (DG) somatotroph adenomas. Mixed SA are further classified into Mammosomatotroph adenomas (MSA), mixed somatotroph-lactotroph adenomas (MSLA) and plurihormonal adenomas.

Similar to other adenomas, SA are soft white to grey macroscopically. MSA are smaller in size with better prognosis compared to MSLA are larger with more invasiveness at the time of presentation.SA are often seen arising from GH expressing pituitary cells in lateral wing of the gland. Extra seller extension of these tumors gives a characteristic shape of snowman.

Microscopically, SA share characteristics of other endocrine tumors: colonies of relatively large monomorphic cells with eosinophilic cytoplasm and spherical nuclei. Disruption of dense reticulin meshwork around the nests of cells distinguishes PA from normal pituitary cells. Hyperplasia to adenoma progression of SA were observed in some cases with familial isolated pituitary adenoma and X-linked acrogigantism syndrome. (WHO 2017) DGSAs are the most common and expresses diffuse cytosolic positively of GH and cytokeratin (CAM 5.2). These are predominantly seen in older age group with slower growth and excellent response to somatostatin treatment. SGSA are less common and behave differently with more aggressive nature like being larger, more invasiveness & proliferation and poor response to somatostatin response. They show co-segregation of cytokeratin and growth hormone granules resulting in characteristic fibrous bodies. These bodies are juxtanuclear keratin aggregates highlighted by cytokeratin immunohistochemical stain (CAM 5.2). MSA are histologically similar to DGSA and ultrastructurally distinct a single cell expressing both GH and PRL granules. MSLA are composed of mixture of two different cells with GH and PRL secreting granules respectively. Either of the cell population can be densely or sparsely granulated with various combinations.

11.2 Clinical manifestations

Growth hormone adenomas are commonly seen in 4th and 5th decades with no gender predominance. More than 60% are macroadenomas compared to other hormonally active tumors and hence have predominant local effects apart from systemic effects. Endocrine systemic effects produce gigantism (pre-pubertal) and acromegaly (after apophyseal fusion). Despite widespread changes including in the appearance, the mean interval between the disease onset and diagnosis is 8.7 years [103].

The facial features described as “beetle brow” appearance include the following changes- deeply furrowed scalp, coarse skin, frontal bossing, fleshy nose, prominent nasolabial folds, thick lips, prognathism, maxillary widening, dental malocclusion with increased inter-dental space and macroglossia with tooth marks on the tongue. The voice changes include low pitched deep voice due to laryngeal hypertrophy and enlarged paranasal sinuses. Hypertrophy of sebaceous glands gives oily appearance to the face. Enlargement of sweat glands gives rise to malodors [104, 105]. Sleep apnea syndrome is seen in up to 75% of acromegalics [106–108].

Enlargement of hands which are thick, fleshy and are classically described as “spade like hands”. The bony hyperostosis and soft tissue thickening causes entrapment neuropathy like carpel tunnel syndrome.

Periosteal new bone formation leads to osteophyte formation, disc degeneration and spinal stenosis. Arthropathy of weight bearing joints is common. Myopathy is a common feature of acromegaly.

Pachydermoperiostosis is a very rare osteoarthrodermopathic disorder whose clinical and radiographic presentations may mimic those of acromegaly and should be considered as a differential diagnosis [109].

The cardiovascular manifestations include hypertension, concentric biventricular hypertrophy and arrhythmias. These changes in the cardiovascular system are least resistant to reversal [110, 111].

Hypertrophy of internal organs like hepatomegaly and splenomegaly is frequently encountered. Diabetes mellitus and islet cell neoplasms are also noted. Oral glucose tolerance is impaired in 50%, while frank diabetes mellitus is seen in 10% of acromegalics. These metabolic changes are however reversible [111].

Colonic malignancies are also documented in patients with GH adenomas [112–114].

Risk factors for colonic malignancies in Acromegaly

1. Age > 50 years

2. Family history of colonic malignancy

3. >3 skin tags

4. Prior colonic polyps

Reproductive abnormalities have also been observed in patients with GH adenomas. These include menstrual disturbances and galactorrhea in women and decreased libido and impotence in men. These effects are due to hyper prolactinemia with mammosomatotrophs or mixed tumors, stalk effect or decrease FSH, LH secretion.

11.3 Endocrine diagnostic criteria

Serum IGF-1 is the initial screening method of choice. The diagnosis is confirmed by the unsuppressed nadir of GH >1 ng/ml and GH > 0.4 ng/ml following 75 gms of OGTT with documented hyperglycemia.

11.4 Criteria for cure

The criteria for cure in GH adenomas are-

1. GH < 1 ng/ml

2. OGTT and GH <0.4 ng/ml done at 12 weeks post-surgery

3. Normalization of somatomedin -C levels

Transsphenoidal surgery is recommended as primary therapy. Experienced pituitary neurosurgeons can achieve the therapeutic goals in 80–90% of patients with microadenomas and 40–60% of those with macroadenomas. The 5-year recurrence rate is approximately 2–8%. Repeat IGF-1 levels and growth hormone levels during an oral glucose tolerance test should be obtained about 12 weeks following surgery, along with an MRI to assess the changes in tumour size. The goal

Drug	Dose	Indication	Side effects
Cabergoline	0.5–2 mg/ week	modest elevations of serum IGF-1 and mild signs and symptoms of GH excess	Nausea, vomiting, constipation, dizziness, headache, compulsive behavior
Octreotide LAR	10–30 mg/ month	significant disease (ie, with moderate-to-severe signs and symptoms of GH excess and without local mass effects)	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia
Lanreotide depot	60–120 mg/ month	significant disease	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia
Pasireotide LAR	20–60 mg/ month	significant disease	Abdominal cramps, flatulence, diarrhea, gall bladder stones and sludge, alopecia, hyperglycemia
Pegvisomant	10–20 mg/ day	significant disease	Hepatotoxicity, nausea, diarrhea

LAR – Long-acting release

Table 4.
Drugs used for medical management of GH excess.

of therapy is to normalize the serum IGF 1 level and reduce the GH levels <1.0 ug/L [115].

Medical management is recommended for patients with persistent disease following surgery. Medical therapy (**Table 4**) may be considered as first line in patients who cannot be cured by surgery, has extensive cavernous sinus invasion, does not have chiasmal compression, or is a poor surgical candidate. If medical therapy is unavailable, unsuccessful, or not tolerated, stereotactic radiotherapy (SRT)/Gamma-knife radiosurgery should be considered unless the technique is not available, there is significant residual tumour burden, or the tumour is too close to the optic chiasm. The response to radiation therapy takes an average of 3.17 years and in the meantime the therapy needs to be bridged with medical management. Remission rates of approximately 60% are observed at 10 years [116].

There is an overall 72% increase in mortality and decrease in 10 years of average life expectancy in patients with acromegaly. Cardiovascular causes are the leading cause accounting for about 25%, while cerebrovascular, malignancies and respiratory diseases are responsible for 15% each. Mortality is 2.4 times higher in females while it is 4.8 times more in males.

Factors associated with increased mortality

1. Older age at diagnosis

2. Male gender

3. Increased disease duration

4. High GH levels [>2.5 ng/ml]

5. Elevated IGF-1 levels

6. Active disease

7. Associated hypopituitarism

8. Associated systemic malignancies

9. Need for radiotherapy for disease control

12. Corticotroph adenoma and Cushing's disease

Of all the pituitary adenomas, the corticotroph adenomas are the most difficult ones to diagnose and treat. The diagnosis revolves between Cushing's syndrome and disease wherein the first one is of non-specific etiology and is produced by any cause of glucocorticoid excess while the latter is due to a pituitary adenoma secreting excess ACTH and thus hypercortisolemia. Cushing's disease is seen in up to 10–16% of all surgically resected pituitary adenomas.

Females are more commonly affected than male, with a M:F ration ranging between 1:3 to 1:10. Though can be seen at any age, is commonly found in 3rd and 5th decade [117].

12.1 Pathology

Corticotroph adenoma (CA) are derived from TPIT-lineage adenohypophysial cells that express ACTH and proopiomelanocortin-derived peptides. These tumors are subdivided into densely granulated CA, sparsely granulated CA and Crooke cell adenoma (CCA) based on secretary granules and cytokeratin accumulation.

More than 80% of the tumors are microadenomas and the rest are macroadenomas. DGCA is the most common subtype in patients presented with Cushing disease. The staining pattern of ACTH granules in SGCA and DGCA are parallel to staining pattern of GH in pure somatotroph adenoma. SGCA are less frequent than DGCA and usually presented as macroadenoma. CCA are rare subtypes, in which cells have typical Crooke hyaline change. These cells are composed of dense perinuclear deposition of cytokeratin filaments appearing as thick hyaline ring. As a result of this rearrangement of cellular organelles and secretary granules to the periphery noted.

12.2 Clinical features

These adenomas are usually microadenomas and seldom cause symptoms of mass effect on the parasellar structures. The main clinical features are due to the hypercortisolemia [118, 119].

1. There is abnormal centripetal fat deposition leading to truncal obesity. The accumulation of fat in the face gives rise to characteristic "moon facies", while the deposition in the supraclavicular area and cervicodorsal region gives rise to "buffalo-hump" appearance.

2. There is thinning of the skin due to atrophy of epidermis and connective tissue. Increased capillary fragility leads to easy bruising and a plethoric face. Purple striae due to stretching of the skin are noted on the abdomen and flanks. Hyperpigmentation and hirsutism are also observed.

3. A multitude of metabolic disturbances are observed in these patients. Hypertension, hyperlipidemia and diabetes mellitus are quite common. Bone

demineralization leading to osteoporosis especially in the vertebral bodies is frequent. Hypocalacemic tetany have also been described. Hypokalemic alkalosis due to mineralocorticoid effect of cortisol on the renal tubules [120].

4. The effects of hypercortisolemia lead to suppression of TSH leading to features of hypothyroidism. Suppression of gonadotropic releasing hormone leads to menstrual disturbances in females, impotence in males and decreased libido in either gender [121–123].

5. Impaired host defences due to hypercortisolaemic effects on the immune system leads to repeated infections ranging from superficial skin infections like tinea versicolor or oral candidiasis to severe life-threatening sepsis [124–126].

6. Psychiatric disturbances range from depression, emotional liability to frank psychosis. Structural changes and cognitive effects have also been observed [127–131].

The case fatality rate in Cushing's disease reaches up to 50% at 5 years, with cardiovascular events leading the cause followed by infections and suicide [118, 132].

12.3 Endocrine evaluation

The first step in a suspected case of Cushing's disease is establishment of the fact that there is a state of hypercortisolaemia and that pituitary adenoma is the cause of it before jumping upon radiological investigations as incidentalomas occur in 10% of cases. Further a detailed evaluation of the medications used to rule out exogenous use of steroids is required.

The biochemical evaluation is to rule out exogenous steroid use by ordering a basal serum cortisol [10].

Step1: Establish hypercortisolaemic state: [133].

a. 24 hours urinary cortisol – this is a simple and sensitive screening measure. This is based on the fact that urinary free cortisol raises exponentially for quantum increases in plasma cortisol. With sensitivity (53–97%) and specificity (86–91%), this is highly useful in patients with high cortisol binding globulins.

b. Elevation of basal plasma cortisol at 11 pm

c. Salivary cortisol measurements at 11 pm is another method to detect cortisol excess and alterations in diurnal variations which are the earliest and subtle biochemical changes, with sensitivity and specificity of 92 and 100%, respectively.

d. Low Dose Dexamethasone test: This is based on the principle of suppression of hypothalamic-pitutitary axis and this decrease in ACTH and morning cortisol levels to <5 micogms/dl by dexamethasone. This was conventionally done by giving 0.5 mgs every 6th hourly for 48 hours before 8 am serum cortisol. This has been replaced by single 11 pm dose of 1 mg of dexamethasone and 8 am serum cortisol measurement.

Step 2: Determine if the cortisol excess is ACTH dependent or independent.

ACTH levels are low (<10 pg./ml) if there is autonomous production by the adrenal gland and the levels are elevated (>20 pg./ml) if a pituitary tumor or ectopic ACTH or corticotropin releasing hormone production is the cause. The level of elevations also give a clue to the cause with moderate elevations of 80–200 pgm/ml seen in corticotroph adenomas while values >200 pg./ml are seen in ectopic ACTH lesions.

Step 3: Distinguishing Cushing's disease from ectopic ACTH states.

The secretory activity of corticotroph adenoma, unlike ectopic ACTH is not autonomous and retains negative feedback responsiveness to glucocorticoid, at higher thresholds. This is the basis of high dose dexamethasone test.

2mgs of dexamethasone is given every 6th hourly for 48 hours and the urinary cortisol is measured. A 50% reduction in urinary cortisol secretion is appropriate suppression and is suggestive of pituitary adenoma. Otherwise, 8–32 mgs of single dose dexamethasone is given at 11 pm and serum cortisol is measured at 8 am. A 50% reduction is suggestive of suppressive response. This has a sensitivity, specificity and diagnostic accuracy of 89%, 100% and 91%, respectively [134].

CRH stimulation test:

The corticotroph adenomas have CRH receptors and hence the levels of ACTH increase following intravenous CRH. A positive response of increase in 50% in plasma ACTH or 20% raise in plasma cortisol is observed in corticotrophs adenomas. Negative results are seen in ectopic ACTH producing lesions as the pituitary corticotrophs are chronically suppressed and are resistant to stimulatory effects of CRH. Diagnostic accuracy of this test is approximately 98% [135, 136].

In some cases, to differentiate between a pituitary vs. an ectopic source of ACTH, inferior petrosal sinus sampling is done, in which catheters are threaded up to the petrosal sinuses that drain the pituitary venous system. ACTH levels are measured from each petrosal sinus and peripherally before and after stimulation with corticotropin-releasing hormone. The basal central to peripheral ACTH >2 is suggestive of corticotroph adenoma while a ratio < 1.7 is suggestive of ectopic ACTH lesion. Following CRH stimulation, a ratio of >3 is diagnostic of corticotroph adenoma with sensitivity and specificity of 96–100%.

The ACTH concentration that exceeds the other side by 1.5 times is likely to be the side of adenoma with sensitivity, specificity and diagnostic accuracy for laterality is 96%, 100% and 78%, respectively [135–138].

12.4 Radiology

As 80–90% of corticotroph adenomas are microadenomas, dynamic contrast MRI of the pitutitary is needed with sensitivity and specificity of 60 and 87%, respectively. Volume interpolated 3D spoiled gradient echo (VI-SGE) helps in detection of microadenoma with a sensitivity and specificity of 87% and 100%, respectively [139–143].

Trans sphenoidal surgery is the initial treatment for an ACTH secreting pituitary adenoma. The remission rates with surgery are 52–96%. The positive predictors for remission following surgery are- 1. Visualisation of adenoma on imaging, 2. Size and extent of adenoma, with microadenomas and without invasion into cavernous sinus faring better and 3. Histopathological confirmation of adenoma. The recurrence rates vary from 15 to 66%. Radiotherapy is the second line of management for persistent or recurrent disease with conventional radiotherapy faring better than stereotactic radiosurgery.

In case of no cure after surgery, or radiotherapy/ stereotactic radiosurgery, medical therapy (**Table 5**), or bilateral adrenalectomy are the options.

13. TSH secreting adenoma

Thyrotroph adenoma (TA) arise from PIT-1 lineage adenohypophyseal cells with chief expression of Thyroid stimulating hormone.

(TSH). These tumors are most infrequent tumors, accounting for less than 2% of all pituitary adenomatous tumors. Excessive secretion of TSH makes thyroid to make excess production of T3 and T4 resulting in hyperthyroidism. An occasional case of TA associated with primary hypothyroidism are reported. The tumor derived from thyroid deficiency are distinct from classical TA clinically, routine microscopy and ultra-structurally.

Patients should be rendered euthyroid with antithyroid drugs like methimazole, propylthiouracil before undertaking transsphenoidal surgery. Patients not cured by surgery can be treated with somatostatin analogues (Octreotide LAR and Lanreotide depot) and by irradiation.

14. Gonadotroph adenoma

Gonadotroph adenoma (GA) are most common pituitary adenoma arise from SF-1 lineage adenohypophysial cell with production of FSH and or LH. These tumors account for highest percentage as clinically non-functioning adenomas. GA are usually macroadenomas with often infiltration into suprasellar and parasellar compartments. Incidental detection of these tumors is increasing these days due to widespread use of CT and MRI. There is a male predominance among middle age and older people. These tumors show a prominent pseudo-rosette pattern around blood vessels mimicking a close diagnosis of esthesioneuroblastoma. Usage of SF-1 immunohistochemistry helps in differentiating these two.

15. Plurihormonal adenoma

Plurihormonal adenomas are also rare adenohypophysial tumours with two or more hormone expressions. They account for 0.9% of all pituitary adenomas. They are morphologically monomorphous with single type of tumours cells, but functionally mixture of different hormone families. There are two subtypes of plurihormonal adenomas, PIT-1 positive adenoma (previously called subtype 3 adenoma) and Adenoma with unusual immunohistochemical combination. Most common of these are Plurihormonal PIT-1 positive adenomas with unusual combination of GH, PRL and TSH. Adenomas with combination of GH and PRL or FSH and LH are not considered as plurihormonal. Adenoma with unusual immunohistochemical combination is unrelated to single cell lineage. For example, combination of GH or PRL with ACTH.

Double adenoma is different from plurihormonal adenomas, existence of two distinct tumor masses in same gland, representing a collision tumor. They tumours are usually incidental tumours, whereas plurihormonal adenomas are macroadenomas.

Silent adenoma presents clinically as non-functioning adenomas, but the surgical resected samples are immunopositive for hormonal factors and their corresponding transcriptional factors. They account for approximately 30% of all pituitary adenomas. To present clinically early, they lack hormonal function. At the time of presentation, several cases tend to exhibit signs of mass effects and few cases with hypothyroidism due to stalk compression or tissue destruction. The diagnosis of

Drug	Mechanism of action	Dosage	Adverse effects
Ketoconazole	Inhibits the side-chain cleavage complex (steroidogenic acute regulatory protein [StAR] and 20,22-desmolase [CYP11A1]), CYP11B1 and 17α hydroxylase/17,20-lyase (CYP17) in the adrenal cortex	200–1200 mg/day	Hepatotoxicity, nausea, dizziness, diarrhea, rash, hypogonadism in men
Etomidate	Blocks multiple steps of steroidogenesis, including CYP11B1, CYP17 and cholesterol side-chain cleavage	0.04–0.05 mg/kg/h	Sedation (avoid overdose [>0.1 mg/kg/h], which will cause apnea and somnolence)
Metyrapone	Inhibitor of steroid 11-β-monooxygenase.	500–4000 mg/day	Hypertension, hirsutism, acne, hypokalemia
Mitotane	a. Adrenolytic action caused by lipid accumulation and atrophy of the fascicularis and reticularis regions of the adrenal cortex b. inhibition of steroidogenesis enzymes such as side-chain cleavage complex, CYP11B1, CYP11B2 and 3β-hydroxysteroid dehydrogenase (3β-HDS) c. increases in cortisol-binding globulin (CBG), reducing free active cortisol	2–5 g/day	Gastrointestinal disturbances, dizziness, cognitive alterations
Osilodrostat (Phase III trial)	potent inhibitor of CYP11B1 Inhibits aldosterone synthase	2–50 mg twice daily	Nausea, headache, fatigue, hirsutism, hypertension, hypokalemia
Levoketoconazole (Phase III trial)	Inhibits side-chain cleavage complex, CYP17, 21-hydroxylase (CYP21A2) and CYP11B1	150–600 mg/day	Nausea, headache, edema, liver enzyme increase, adrenal insufficiency
Nevanimibe (Phase II trial)	cholesterol acyltransferase 1 inhibitor	Under study	Under study
Abiraterone acetate (Phase II trial)	Inhibits CYP17 and CYP21A2	250–500 mg twice daily	Hypertension, hypokalemia, adrenal insufficiency
Pasireotide	Targets four of five SSTR subtypes, with highest affinity for SSTR5, followed by SSTR2, SSTR3, and SSTR1 and reduces ACTH secretion	600–900 μg twice daily. LAR: 10–30 mg/month	Diarrhea, nausea, cholelithiasis, hyperglycemia
Cabergoline (Off-label)	Dopamine receptor type 2 Agonist Reduces ACTH secretion	0.5–7 mg/week	Nausea, dizziness, compulsive behaviour
Temozolamide (Off-label)	DNA alkylation	150–200 mg/m2/day for 5 days each month per cycle	Fatigue, hearing loss, liver enzyme increase, cytopenia

Table 5.
Drugs used in the treatment of Cushing's syndrome.

silent adenoma is exclusively based on immunohistochemical markers against transcriptional factors and hormones expressed. The morphology of these tumors corresponds to those of their functioning counterparts. The characterization of silent adenoma is important as they determine prognosis. For e.g.: Silent Corticotroph adenoma is associated with aggressive behavior of early recurrence rate when compared to other silent tumors.

Atypical adenoma is defined as tumor cells with extensive nuclear staining for p53, high mitotic index and Ki-67 proliferative index >3%. The prognostic activity related to proliferation of pituitary tumors are extensively studied in the last two decades. But, the significance of proliferation markers or correlation with tumor invasiveness and recurrence could not be established using above classification. Ki67 labelling is not predictive factor for recurrence risk, but could be a useful predictor of progression risk in tumor remnants. Hence, in new classification the term atypical adenomas are no longer used. The best prognosticator still remains the tumor invasiveness hormone produced and subtype of particular adenoma.

16. Follow up of patients with pituitary adenoma

The frequency of testing and the criteria for remission/cure for patients undergoing treatment for pituitary adenoma are elaborated in the **Table 6** [144].

Tumor type	Tests	Timing of tests	Interpretation
Corticotroph adenoma	Morning serum cortisol 24 hours urinary free cortisol(UFC)	Within 7 days of surgery	< 5 ug/dL (138 nmol/L) UFC < 28–56 nmol/d (<10–20 ug/d)
GH secreting adenoma	Serum IGF 1 Random GH GH after oral glucose load MRI	12 weeks after surgery	IGF 1– normal(remission) serum GH <0.14 ug/L suggests "surgical remission," serum GH <1 ug/L indicates "control serum GH > 1 ug/L – measure GH nadir after glucose load
Prolactinomas	Serum prolactin MRI	After 2 years of therapy	Serum prolactin every 3 months for the first year after completion of therapy and annually thereafter MRI if there is increase in serum prolactin
TSH secreting adenoma	TSH T3 suppression test	One week after surgery	Undetectable TSH and positive T3 suppression test with undetectable TSH and no response to TRH (or central hypothyroidism)

Table 6.
Follow up and remission criteria for patients with pituitary adenoma.

17. Pituitary apoplexy

Pituitary apoplexy, is a clinical syndrome with incidence ranging from 4 to 20%, due to varying defining clinical criteria and presentation, ranging from subclinical to life threatening situation. It is a serious yet rare condition affecting the patients with pituitary lesions. Apoplexy is referred to as acute infarction of pituitary gland with or without haemorrhage. Usually, patients present due to sudden haemorrhage in adenoma and less often with bleed within infarcts or in the cystic lesions like Rathke's cyst. The rapid expansion of sellar contents manifests classically as headache, visual disturbances, and varying features of hypopituitarism [145, 146].

17.1 Pathogenesis

Varying pathophysiological mechanisms have been postulated for the occurrence of pituitary apoplexy- (1) rapid growth of the tumour outgrowing the vascular supply, (2) compression of the superior hypophyseal trunk along the stalk, (3) intrinsic vasculopathy with incomplete maturation of the basal membrane and (4) overexpressed VEGF leading to risk of haemorrhage.

17.2 Precipitating factors

Though most often pituitary apoplexy occurs without any external precipitating events, few events like a head injury, coughing/sneezing, idiopathic thrombocytopenic purpura, spinal anaesthesia, radiotherapy, pregnancy have been implicated. Medications like anti-platelet drugs, anti-coagulants, clomiphene, leuprolide, goserlin and oestrogen have been implicated. Bromocriptine and cabergoline administered for prolactinomas have also been reported to have precipitated pituitary apoplexy.

17.3 Grading of pituitary apoplexy

The first grading of pituitary apoplexy was suggested by Rajashekaran et al., in their seminal work of guidelines suggested a scoring system from 0 to 10, which included level of consciousness (0–4), visual acuity (0–2), visual field defects (0–2) and ocular palsies (0–2). They proposed such objective scoring system to monitor conservatively managed patients and assess the effect of surgical intervention, with a long-term aim of a randomised control trial for validation of management [147]. Giritharan et al. (2016) applied this scoring system retrospectively to their database of cases with apoplexy and observed that lower PAS grades could be managed conservatively while higher grades required immediate surgical intervention [148].

Jho et al. (2014) [149] proposed a severity grading system based on clinical and imaging features into a 5-grades: (1) Grade 1- asymptomatic (subclinical); (2) Grade 2- only endocrine symptoms; (3) Grade 3- presence of headache; (4) Grade 4- ocular palsies; (5) Grade 5- Visual deficits or altered consciousness not allowing testing for visual deficits. They had further 3 clinical subgroups or modifiers (p, r, s) wherein the presence of prolactinoma(p), Rathke's cyst (r) with haemorrhage and co-morbidities/sick (s) were preferentially managed medically. They reviewed their database of over 20 years and proposed algorthimic based treatment with immediate surgery for higher grades and conservative/medical management for lower grades.

17.4 Imaging in pituitary apoplexy

MRI of the brain is the current modality of choice for pituitary apoplexy. MRI is much superior to CT in the diagnosis of pituitary apoplexy with a sensitivity ranging from 88–90% [145, 150]. The signal intensity changes depend upon the changes in the haemoglobin or in turn the age of the bleed.

Fluid–fluid level sign can be seen in old bleeds with supernatant T1W hyperintense upper/anterior fluid level corresponds to extracellular met Hb, while the lower/posterior iso to hypo intense area is related to sedimented blood products [151].

Thickening of mucosa in pituitary apoplexy was demonstrated by Arita et al. [150] in 9 of their 11 patients at 7 days, which was predominantly in the compartment below the sella and was postulated to be due to venous congestion.

Histopathological examination of the mucosa in those who underwent transsphenoidal resection swollen subepithelial layer of mucosa. In others, a repeat MRI showed complete resolution without any treatment. Mucosal thickening does not preclude a transsphenoidal surgical approach.

Sheehan syndrome refers to postpartum apoplexy and usually occurs in women having suffered postpartum hemorrhage and hypovolemia. It is hypothesized that hypertrophied pituitary gland is more susceptible to infarction from hypovolemia.

18. Recurrent pituitary apoplexy

Recurrent pituitary apoplexy, is a rare event described by several authors as few case reports. The prominent one is by Houseman et al. (2019) wherein they retrospectively analysed their data of 798 surgically treated patients over a period of 27 years and found that apoplexy was noted in 76 patients. There were only 4 patients (5.3%) who had recurrent episodes of apoplexy. These haemorrhagic recurrences were noticed when the Knosp's score was more than 4, implying complete encasement of ICA and hence incomplete tumor resection (8%) in the cavernous sinus (23.5%). Brown et al. (2020) described a single case of multiple episodes of pituitary apoplexy over 11 years, which interestingly has varying phenotypes changing from silent gonadotropic to silent corticotroph adenoma. The MIB-1 index was however, consistently high at 10%. Teasdale et al. (2015) described recurrent pituitary apoplexy following development of a neoplasm adjacent to the sella. Tumour residue or recurrence are the major factors responsible for recurrent pituitary apoplexy and need a close follow-up. The management is similar to any other pituitary apoplexy which includes stabilisation of general and hormonal status. Surgical decompression of the hematoma and the residual tumour is the treatment of choice, followed closely by hormone replacements. Follow-up imaging to look for residual/recurrent tumour and radiotherapy. A further look into the molecular markers predisposing to recurrent haemorrhages to be looked in future [152–160].

19. Conclusion

- Pituitary neoplasms are common intracranial tumours accounting for approx. 15% of all intracranial tumours.
- The pituitary neoplasms are believed to originate due to aberration in the normal growth and differentiation of pituitary stem cells. The detection of the pituitary specific transcription is now the basis of the recent most WHO classification.
- The clinical manifestations of such tumours are due to- hormone excess, deficiency of other pituitary hormones, pressure effects on optic pathways, surrounding brain parenchyma, ventricular system, paranasal sinuses and systemic.
- The diagnosis and management require a close collaboration between endocrinologist, radiologist, neurosurgeon, pathologist and radiation oncologist.
- The goals of therapy include- hormonal remission, decompression of neural elements, restoration/replacement of deficient hormones, maximising tumour remission.

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