Endocrinal Dysfunction in Pituitary Tumors

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Introduction

Prolactinomas and nonfunctioning adenomas are the most common types of pituitary tumors [1]. They may present initially with symptoms of endocrine dysfunction such as infertility, decreased libido, and galactorrhea, or with neurologic symptoms such as headache and visual changes. The diagnosis may also be made incidentally; the so called pituitary incidentaloma. Oversecretion of hormones from a dysfunctional pituitary tumor may result in classic clinical syndromes, the most common of which are hyperprolactinemia, acromegaly, and Cushing disease. In the diagnostic approach to a suspected pituitary tumor, it is important to evaluate complete pituitary function, because hypopituitarism is common. Therapy for pituitary tumors depends on the specific type, and should be managed with a team approach to include endocrinology and neurosurgery [2].

Anatomy and physiology

The pituitary gland lies in the sella turcica at the base of the skull. Despite its central role in the endocrine system, the pituitary is extremely small—about the size of a pea—and weighs only about 0.5 g. It is divided into anterior (adenohypophysis) and the posterior (neurohypophysis) lobes. The 2 lobes can almost be considered as entirely different glands. The anterior lobe originates from the oropharynx (Rathke's pouch) and meets tissue of neural origin (from the hypothalamus) growing inferiorly forming the posterior lobe [3]. The pituitary stalk connects the hypothalamus to the pituitary gland and serves to transmit the axons of the hypothalamus to the posterior lobe; it also transmits regulatory hormones from the hypothalamus to the anterior lobe via a portal system. The anterior lobe represents approximately two-thirds of total pituitary volume. The optic chiasm rests approximately 5 to 10 mm above the diaphragma sella [4].

The pituitary gland controls the function of many other endocrine glands, often being referred to as the "master gland." The pituitary secretes at least eight hormones that regulate organ function and are critical to survival [4].

A- Anterior Pituitary

The anterior pituitary is a glandular secretory organ. The anterior pituitary is composed of three cell types: acidophils, basophils (often collectively referred to as chromophils), and chromophobes. The chromophils are the principal secretory cell types whereas the chromophobes are not thought to have secretory function [4].

Today, five cell types producing the six major hormones are best differentiated using immunohistochemical staining. These are:

1. Mammotrophs, which produce PRL (acidophilic)

2. Somatotrophs, which produce GH (acidophilic)

3. Corticotrophs, which produce ACTH, MSH, and various endorphins (basophilic)

4. Thyrotrophs, which produce TSH (basophilic)

5. Gonadotrophs, which produce FSH and LH (basophilic)

In general, the balance of releasing factors secreted by the hypothalamus and inhibiting factors secreted by each hormone's target organ control the secretion of each hormone produced by the anterior pituitary. The releasing and inhibiting factors for each hormone are summarized in Table 1. The exception to this principle is prolactin, which is under tonic-inhibition by dopamine secreted by the hypothalamus. The hypothalamus secretes releasing factors into a primary capillary plexus from which they travel to a secondary capillary plexus in the anterior pituitary [4].

Pituitary adenomas are classified based on their functional status (nonfunctioning vs hormonally active) and size (tumors up to 1 cm in diameter are microadenomas, whereas tumors greater than 1 cm are macroadenomas) [4].

Table 1. Major Hormones of the Anterior Pituitary [4].

Hormone	Target	Effects on Target	Downstream Effects
PRL	Breast	Lactation	—
GH	Liver, skeleton, soft tissues	IGF-1 secretion (from liver); growth and regulation of nutrient metabolism	IGF-1 is primary mediator of growth
ACTH	Adrenal gland	Induction of cortisol secretion	Metabolism regulation; resistance to physiologic stress; maintenance of vascular tone
TSH	Thyroid gland	Induction of thyroid hormone (T4) secretion	Metabolism regulation
FSH and LH	Testes/ovaries	Secretion of testosterone or estrogen/progesterone	Maintenance of fertility, lean body mass, and bone density

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; PRL, prolactin; TSH, thyrotropin-stimulating hormone.

Anterior lobe tumors

Essentially all cases of hyperpituitarism occur secondary to pituitary adenoma. These tumors are commonly encountered in clinical practice. They represent approximately 10% of diagnosed brain neoplasms, and as many as 20% of people have a pituitary tumor on postmortem examination, suggesting that most pituitary adenomas are asymptomatic [5].

Although the majority of pituitary adenomas are asymptomatic, most tumors present in three discrete ways:

1. Hormonal hypersecretion,
2. Local mass effects (including pituitary hypofunction due to compression of the normal gland), or
3. Incidental discovery during cranial imaging for an unrelated condition.

Approximately 75% of pituitary tumors are "functioning" and produce a single predominant hormone; these patients typically present with the signs and symptoms of hormone excess. For example, patients with a TSH-secreting adenoma have pituitary hyperthyroidism and present with the signs and symptoms of hyperthyroidism [6].

The mass effects can be extensive and problematic given the location of the pituitary gland. Patients can present with varying degrees of hypopituitarism secondary to compression of normal anterior pituitary. Up to 90% of patients with nonfunctioning pituitary macroadenomas exhibit deficiencies in at least one pituitary hormone with formal testing [7]. Thus, while it is easy to focus on the signs and symptoms of glucocorticoid excess in a patient with Cushing disease, for example, the patient might also suffer from pituitary hypothyroidism. Prolactin is frequently elevated in all varieties of pituitary tumors secondary to disruption in normal inhibitory tone from the hypothalamus. Regardless, posterior pituitary dysfunction is unusual,

even among patients with very large tumors. Once hormonal abnormality is confirmed then MRI of the sella should be performed. Dedicated pituitary protocol MRI with 1.5-mm cuts provides clear definition of hypothalamic/pituitary anatomy; the addition of contrast is recommended and enhances detection of small pituitary tumors [8].

Table 2: Pituitary hypersecretion syndromes [4].

Condition	Presentation	Important Considerations
Prolactinoma	Galactorrhea, hypogonadism	Medication history critical; surgery reserved for patients who fail medical therapy
Acromegaly (Excess GH)	Soft tissue overgrowth, hyperhidrosis, HTN, DM2	IGF-1 is preferred diagnostic test
Cushing disease (Excess ACTH)	Centripetal obesity, pigmented striae, insomnia, mood lability, skin thinning, proximal muscle weakness, HTN, DM2, hypogonadism	Presentation can be subtle and diagnosis challenging
TSH secreting adenoma	Weight loss, heat intolerance, hyperdefecation	Diagnosis suggested by hyperthyroid symptoms with excess fT4 and high (or inappropriately normal) TSH

Abbreviations: ACTH, adrenocorticotropic hormone; DM2, diabetes mellitus type 2; FT4, free T4; GH, growth hormone; HTN, hypertension; IGF-1, insulin-like growth factor 1; TSH, thyrotropinstimulating hormone.

1. Abnormalities of Prolactin Secretion

a. Hypersecretion (Prolactinoma)

Prolactinomas are the most frequently observed type of hyperfunctioning pituitary adenoma, representing 20% to 30% of all clinically recognized pituitary tumors and half of all functioning tumors. Despite their frequency, prolactinomas are not associated with significant mortality. In women, hyperprolactinemia causes amenorrhea, galactorrhea, loss of libido, and infertility. In men, symptoms are relatively nonspecific and include decreased libido, impotence, premature ejaculation, erectile dysfunction, and oligospermia [9].

Diagnosis of Prolactinoma

Diagnosis of prolactinoma is straightforward when prolactin is markedly increased (eg, >500 mg/L) with a visible pituitary adenoma on MRI. In general, prolactin levels parallel tumor size; most prolactinomas greater than 1 cm have prolactin concentrations greater than 250 mg/L [10]. Hyperprolactinemia in the absence of a pituitary tumor should prompt assessment for other causes of hyperprolactinemia.

Table 3: Common non-tumoral causes of hyperprolactinemia [4].

Physiologic	1. Pregnancy 2. Stress 3. Lactation/nipple stimulation 4. Primary hypothyroidism
Pharmacologic	1. Antipsychotics (1st and 2nd generation) 2. Antidepressants (TCA, SSRI) 3. Anti-emetics (metoclopramide, prochlorperazine) 4. Opioids, verapamil
Miscellaneous	1. Chest wall trauma/irritation (zoster, surgery) 2. Renal failure (PRL renally cleared)

Abbreviations: SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Drug-induced hyperprolactinemia is relatively common; increases are typically less than 200 mg/L [11]. Hyperprolactinemia can also occur with any large sellar lesion as a result of compression of the pituitary stalk and subsequent interference with dopamine inhibitory signaling from the hypothalamus. This so-called "stalk effect" usually results in modest hyperprolactinemia (levels typically <100 mg/L) [12]. Some prolactin immunoassays can result in falsely lowered prolactin values via a well-known phenomenon ("hook effect"); hence, many recommend diluting serum samples followed by reassessment of prolactin in cases of macroadenomas with mild increases in prolactin [13].

Treatment of prolactinoma

1- Surgical treatment

As in all pituitary tumor types, surgery remains a treatment option in prolactinomas. Surgery has been the preferred therapy of prolactinomas until the mid-1980s, when bromocriptine (BRC) was shown to be effective not only in controlling PRL levels but also in successfully shrinking tumor mass. Therefore, indications for surgery in patients with prolactinomas are the following: (1) patients with pituitary apoplexy, which is a potentially life-threatening clinical syndrome caused by infarction or haemorrhage into an existing pituitary tumor [14]; (2) failure of medical therapy; (3) expanding prolactinomas [15].

Within these indications, the trans-sphenoidal approach represents the standard of care for macroprolactinomas and most microprolactinomas [15]. Craniotomy must be reserved for tumors inaccessible via the trans-sphenoidal approach, and currently is indicated in extremely rare cases. Moreover, in patients with giant and invasive prolactinomas, surgery can hardly be curative. Therefore, in these cases, the goal of surgery is to debulk the tumor to improve the symptoms related to mass effects [15]. Recent technological advances have proposed minimally invasive endoscopic techniques in the setting of trans-sphenoidal surgery. The main advantage afforded by endoscopy is the superior panoramic view. Endoscopy provides some additional benefits, including avoidance of sub-mucosal trans-septal dissection, thus eliminating nasoseptal perforations, less patient discomfort due to the lack of nasal packing and reduced operative time and hospital stay [16].

2- Medical therapy

Dopamine agonists can be divided into two classes: the ergot derivatives, like bromocriptine, pergolide and cabergoline, and the non-ergot derivatives, like quinagolide. Treatment with dopamine agonists decreases the size of prolactinomas through a number of mechanisms. *First*, by reducing cell volume through inhibition of hormone secretion in an early phase; *second*, via inhibition of prolactin synthesis at a later stage; and *finally*, by inducing perivascular fibrosis and cell necrosis [17].

Bromocriptine (Parlodel)

Bromocriptine, is the oldest drug for medical treatment of prolactinomas [15]. It has D2 receptor agonist and D1 receptor antagonist properties. It is still frequently prescribed as the best alternative to cabergoline [18]. Compared with cabergoline, bromocriptine has a shorter half-life and is administered two or three times daily. The therapeutic dose generally ranges between 2.5 mg and 15.0 mg per day, with most patients receiving 7.5 mg or less. In patients with treatment resistance, the doses can be increased to 20–30 mg per day [19].

In 80–90% of microprolactinomas and in 70% of macroprolactinomas, bromocriptine controls hyperprolactinemia and restores gonadal function and reduces tumor size [20]. Tumor mass effects, such as headaches and visual field defects, improve within days after initiation of

bromocriptine therapy in most patients. However, treatment withdrawal can often result in recurrence of hyperprolactinemia [21].

Cabergoline (Dostinex)

Cabergoline is a selective D2 receptor agonist with widely known beneficial effects in resolving hyperprolactinemia [22]. Chronic cabergoline treatment at a twice-weekly dose of 1 mg significantly reduces serum prolactin levels in up to 95% of women with hyperprolactinemia. In a comparative retrospective study by Di Sarno et al, the efficacy of cabergoline was demonstrated to be greater than that obtained using bromocriptine [21].

At treatment start, the dose of cabergoline is usually 0.5 mg per week in patients with idiopathic hyperprolactinemia or microprolactinomas. For individuals with macroprolactinomas, treatment should be initiated at very low doses (0.25 mg weekly) to avoid too rapid tumor shrinkage, as this can cause apoplexy [21]. The dosage is then increased according to the individual patient's condition in order to control prolactin excess. After 12–24 months of cabergoline therapy, a reduction in tumor mass is observed in >80% of cases, whereas total tumor disappearance occurs in 26–36% of patients. The efficacy of cabergoline treatment has been demonstrated in male patients, not only for the control of prolactin levels and tumor size, but also for the improvement of fertility by normalizing sperm quality and sexual function [23].

Some studies have reported negative effects of cabergoline on cardiac valves but the investigators conclude that data published are inconclusive. Importantly, withdrawal of cabergoline therapy has been associated with improvement or no further deterioration of cardiac valve disease [24]. Table 4 shows the criteria for Cabergoline withdrwal.

Table 4 Criteria for cabergoline withdrawal [25]:

1. Serum prolactin levels in the normal range (<1,087 pmol/l, equal to 25 μg/l, in women and <652 pmol/l, equal to 15 μg/l, in men) during treatment with cabergoline (minimal treatment duration: 2 years)
2. No remnant tumor visible on MRI or a reduction in tumor size by ≥50% compared with baseline size during treatment with cabergoline (minimal treatment duration: 2 years)
3. In case of tumor persistence, patients are considered for withdrawal of cabergoline only if the outer border of the tumor is ≥5 mm or more from the optic chiasm, without evidence of invasion of one or both cavernous sinuses or any other critical area
4. To minimize the risk of errors in reading MRI scans, all patients continued to receive cabergoline therapy for 12 months after fulfilling the withdrawal criteria and before withdrawal of the medication (total minimal treatment duration: 3 years before withdrawal)
5. Patients were required to continue follow-up after withdrawal for at least 24 months

Quinagolide (Norprolac)

Quinagolide, a non-ergot derived dopamine agonist with selective D2 receptor activity, is available for oral administration in a single daily dose. It is reported to control prolactin excess and tumor growth [26]. It might be considered as effective as bromocriptine, however, the safety profile was more favorable for quinagolide [21]. Compared with cabergoline, quinagolide was less effective and adverse effects were more frequent, although quinagolide does not seem to induce cardiac valve disease [27].

Pergolide (Permax):

Lamberts and Quik [28] did not report any superiority of pergolide over bromocriptine in

lowering serum prolactine levels and in inducing tumor shrinkage. Pergolide was withdrawn from the market in 2007 because of adverse effects on cardiac valves [21].

Novel treatments:

Temozolamide may be helpful for the treatment of aggressive prolactinoma or carcinoma [29]. New therapeutic targets for the treatment of prolactinoma, such as estrogen receptor alpha [30] or epidermal growth factor receptor 2 are also being investigated [31].

3- Radiotherapy

Indication for radiotherapy is essentially resistance to dopamine agonists and surgery, with a proven trend to growth [32].

b. Prolactin deficiency

Hypoprolactinemia is found in patients who have mutations of the transcription factors, but in patients who have structural pituitary disease, it is a marker of severe pituitary damage [33, 34]. In women, prolactin deficiency can cause failure of lactation in the postpartum period but a phenotype attributable to prolactin deficiency in man has yet to be established [35].

2. Abnormalities of Growth Hormone Secretion

a. Hypersecretion (Gigantism and Acromegaly)

Hypersecretion of growth hormone leads to increased production of insulin-like growth factor 1 (IGF-1) by the liver. Children in whom the epiphyses have not closed experience gigantism. In contrast, acromegaly develops in adults. Cardiac disease, hypertension, and ventricular hypertrophy are the most important causes of morbidity and mortality in acromegalic patients. Patients with acromegaly have a characteristic facies as the soft tissues of the nose, mouth, tongue, and lips become thicker. Airway obstruction and obstructive sleep apnea can affect up to 70% of acromegalic patients [36] and can cause perioperative airway compromise [37].

Laboratory Diagnosis of Acromegaly

The diagnosis is often delayed by years due to insidious onset [38]. Assessment for GH oversecretion should be considered in patients with suggestive clinical features and is mandatory in any patient with a pituitary adenoma [39]. Measurement of IGF-1, a growth factor produced in the liver in response to GH stimulation, is the recommended screening test for GH oversecretion [40], and a normal IGF-1 level essentially excludes the diagnosis of acromegaly. The pulsatile nature of GH secretion makes a random GH an unreliable means of diagnosing acromegaly [41].

Once an increase in IGF-1 is demonstrated the diagnosis should then be confirmed with dynamic testing involving oral glucose loading (oral glucose tolerance test), typically done under the supervision of an endocrinologist. This test relies on the ability of hyperglycemia to suppress GH secretion in normal individuals while lack of GH suppression is characteristic of acromegaly [42].

Treatment of Acromegaly

Currently, therapeutic modalities for acromegaly include neurosurgical intervention, medical therapies, and radiotherapy [43].

Surgery for acromegaly

In view of the known complications of GH excess, treatment of all patients with acromegaly is indicated. Transsphenoidal adenomectomy is the treatment of choice for GH-secreting

adenomas. The goals of treatment should include: normalizing GH-secretion, preserving normal pituitary function and reversing the mechanical compression. These goals can be achieved in approximately 50% of patients after adenomectomy.

After complete surgical removal of the tumor, plasma IGF-I and both basal GH concentrations and its responses to dynamic stimulation become normal. Recurrences in these patients are rare with prolonged follow-up. The main predictors of outcome after surgery include tumor size and location, preoperative GH concentrations, and the expertise of the surgeon [44, 45] while the most sensitive predictor remains a GH concentration within the first week after operation that is less than 2 μg/l [46].

Medical treatment of acromegaly [9].

Somatotroph pituitary adenomas predominantly express somatostatin receptor (SSTR) types 2 and 5. At the level of the pituitary, the main effect of somatostatin is the inhibition of both hormone secretion and cell growth. Medical therapy, such as somatostatin receptor ligands (SRLs) and dopamine agonists or the GH-receptor antagonist pegvisomant target pituitary adenoma GH secretion or block peripheral GH action, respectively, and are mostly used to treat persistent or recurrent acromegaly after noncurative neurosurgery [43]. SRLs are classified as first-generation (predominantly acting on SSTR; octreotide and lanreotide) and second-generation or multiligand acting on SSTR5 and SSTR2 (pasireotide). Table 5 shows the clinically available medications for acromegaly.

Table 5 Commercially available medical therapy for acromegaly [43]:

Drug	Mechanism of action	Commercial name
Octreotide and octreotide LAR	Predominantly SSTR2 SRL	Sandostatin Sandostatin LAR/LAR depot
Lanreotide, lanreotide SR, and lanreotide autogel	Predominantly SSTR2 SRL	Somatuline autogel
Pasireotide LAR	SSTR5 . SSTR2 . SSTR3 . SSTR1 multireceptor SRL	Signifor LAR
Pegvisomant	GH-receptor antagonist	Somavert
Cabergoline	D2DR agonist	Dostinex
Bromocriptine	D2DR agonist	Parlodel

Abbreviations: LAR, long-acting release; SSTR, somatostatin receptor; SRL, somatostatin receptor ligand; SR, slow release; D2DR, D2 dopamine receptor; GH, growth hormone.

Maison et al published a meta-analysis of the role of *cabergoline* in acromegaly [47]. This study had considerable limitations and concluded that cabergoline has a modest efficacy in acromegaly. The positive effect is also seen in patients with normal PRL levels.

As regards treatment with somatostatin analogs, a study where 32 patients with de novo acromegaly were treated with *octreotide* 20 mg/28 days for six months before surgery has been published. Biochemical reduction was achieved in one third of patients, and significant tumor reduction in two thirds of patients [48]. New presentations of octreotide hydrogel implants have shown good safety and efficacy results [49]. Mercado et al discontinued treatment with somatostatin analogs in patients who had been controlled for at least two years, a strategy similar to that used in prolactinoma, but leading to a high biochemical recurrence rate in acromegaly [50].

Another study reported the use of combined treatment with somatostatin analogs and *pegvisomant*, an injectable, genetically engineered, analogue of human GH that blocks the action of GH, with good results and few side effects [51]. The results of the ACROSTUDY, conducted on 1288 patients treated with pegvisomant and mainly intended to assess treatment safety, were reported. Liver function impairment was found in less than 1% of subjects and consisted of transaminase increase to three times the upper limit of normal. An increased adenoma size was reported in 3.2% [52].

b. Growth hormone deficiency

GH deficiency causes a variety of signs and symptoms determined by the age at which patients present. A neonate who has congenital GH deficiency or hypopituitarism presents most frequently in the first 24 hours of life with severe hypoglycemia often associated with convulsions. Other features of GH deficiency during the neonatal period are prolonged conjugated hyperbilirubinemia, hypothermia, and, in boys, possibly a micropenis [53].

Older babies may present with failure to thrive and poor weight gain. Older children present with short stature and reduced growth velocity for their age. Those who have severe GH deficiency develop a characteristic appearance with a prominent forehead and depressed midface development caused by the lack of GH effect on endochondrial growth at the base of the skull, occiput, and sphenoid. Dentition may be delayed. Other features may be present that are attributable to the underlying etiology of the GH deficiency [35].

Patients who have childhood-onset GH deficiency do not seem to suffer the same degree of impairment in quality of life as those who have adult-onset GH deficiency [54].

In contrast to GH-deficient neonates who present with hypoglycemia, adults are insulin resistant and the serum lipid profile is abnormal, with elevated total and low-density lipoprotein (LDL) cholesterol and triglyceride levels [55].

GH-deficient patients have bone mineral density (BMD) that is reduced compared with healthy controls [56]. These changes are age dependent and evident particularly in young adults. Fracture risk is increased in GH-deficient adults [57, 58].

Treatment of GH deficiency

There is a debate regarding the selection of patients for GH replacement. Practice varies between countries and is influenced by availability of funding for treatment. In UK, patients are selected according to one or more of a number of specific criteria outlined below [59]:

- Peak GH response <3μg/L to the insulin tolerance test (ITT).
- Patient already receiving full supplementation of other deficient hormones, as required.
- Reduced Quality of Life.
- An adverse cardiovascular risk profile and/or osteopenia have been demonstrated.

Patients should have severe GH deficiency by ITT, glucagon, arginine, or alternative tests such as arginine plus growth hormone releasing hormone (GHRH) [59].

When the indication for GH-replacement has been ascertained, the patient is commenced treatment usually by a low initial dose, dependent on age, since adolescents may benefit from higher initial doses, as will also women on oestrogen therapy [60]. The dose titration is monitored by IGF-I concentrations [61, 62, 63], and a number of organ end points, which may act as 'biomarkers' of the treatment effects.

Patients are commenced on 0.2 mg somatotrophin subcutaneously once a day initially. The dose is reviewed every two weeks according to clinical response, serum IGF-I and any side effects and the dose is increased if necessary at 4 weekly intervals until the maintenance level, aiming at an age adjusted IGF-I [62]. A sustained release once weekly growth hormone preparation is currently undergoing clinical trials and may be an alternative in the future [64].

GH replacement therapy has been proposed for children with persistent GH deficiency after treatment of Cushing's's disease in order to favor the "catch-up" growth and to ensure the achievement of final height. GH replacement was shown to be effective in improving body composition and cardiovascular risk profile in adults with post-Cushing's GHD [65].

3. **Abnormalities of ACTH Secretion**

   a. *Hypersecretion (Cushing Disease)*

Cushing disease results from the hypersecretion of ACTH by a pituitary adenoma and consequent hypercortisolism. Systemic hypertension is among the most common manifestations by a variety of mechanisms [6]. Secondary to hypertension, a high prevalence of left ventricular hypertrophy and concentric remodeling has been reported. Glucose intolerance occurs in at least 60% of patients, with overt diabetes mellitus (DM) present in up to one third of all patients. Patients are typically obese with characteristic "moon facies." Despite the association with obstructive sleep apnea, endotracheal intubation is not usually more difficult [37].

Diagnosis of Cushing's Disease

The proper diagnosis of Cushing's syndrome (hypercortisolism) can be challenging and requires repeated assessment of endocrine function. Most cases of Cushing syndrome are caused by excess ACTH secretion from a pituitary adenoma (Cushing disease) [66]. The primary issue likely to be encountered by skull base surgeons is whether a patient with a known pituitary adenoma (usually incidentally found) could have Cushing's disease. This is a critical distinction to make because management of Cushing's disease includes surgical resection; whereas, there may be no acute indication for surgery with a small nonfunctional adenoma.

In general, only patients with multiple and progressive clinical features of hypercortisolism should be considered for biochemical screening [67]. Before undertaking a biochemical evaluation, a thorough history is essential as exogenous glucocorticoid use represents the most common cause of clinical hypercortisolism "iatrogenic Cushing's" [68]. Endogenous hypercortisolism from Cushing's disease is characterized by loss of appropriate feedback control on ACTH secretion. These characteristics can be assessed using 3 biochemical tests:

   (1) 24-hour urinary free cortisol (UFC) excretion (assesses total cortisol production),

   (2) late night salivary cortisol collection (assesses whether diurnal rhythm is present),

   (3) 1 mg dexamethasone suppression test.

Diagnosis of Cushing's syndrome via these tests typically occurs in conjunction with an endocrinologist; a referral to an endocrinologist should be considered for any patients with a history of, or physical features suggestive of, hypercortisolism.In general, at least 2 tests must be unequivocally abnormal (eg, 24 h UFC >3x upper limit of normal) to establish the diagnosis of Cushing's syndrome [67].

Conclusively establishing the diagnosis of Cushing's disease can be challenging. Patients with unequivocally positive screening tests should have ACTH measured (to confirm the pituitary origin of hypercortisolism) followed by MRI of the pituitary. In cases where MRI is equivocal, then several options to localize ACTH overproduction to the pituitary exist, including high-dose dexamethasone suppression tests or sampling of ACTH levels in the inferior petrosal sinus [69]. While invasive, inferior petrosal sinus sampling has a sensitivity and specificity of greater than 90% and is the preferred option at pituitary centers where technical expertise and experience exists.

Treatment of Cushing's syndrome

Surgery

Transsphenoidal selective tumor resection (TSS) is the optimum initial treatment of Cushing's disease, meeting all therapeutic goals [70, 71]. The success of TSS depends on the surgeon's

expertise because tumors might be small, difficult to recognise, or have dural invasion; piecemeal resection seems less successful than the histological pseudocapsule technique [72]. TSS complications are more likely to occur with macroadenomas or extensive pituitary exploration. Second pituitary surgery is a good option when residual tumor is visible or has regrown but is not invasive [70, 71, 73].

Medical therapy

Indications for medical treatment of Cushing's syndrome include:

1. acute complications of hypercortisolism (psychosis, and infection)
2. surgery pretreatment in severe cases if surgery is delayed
3. hypercortisolism after unsuccessful surgery, while awaiting control from radiotherapy; unresectable or metastatic tumors
4. hypercortisolism due to an occult ectopic ACTH-producing neuroendocrine tumor [74].

Treatments include steroidogenesis inhibitors, tumor-directed drugs, and glucocorticoid receptor antagonists [74]. A combination of drugs may be necessary to achieve eucortisolism [75].

The antifungal ketoconazole can decrease cortisol production at doses of 400–1200 mg/day [76]. The most important side-effects of ketoconazole are hepatotoxicity, gastrointestinal complaints, and hypogonadism (in men) [74, 76].

Corticotroph adenomas can express dopamine (D2) and somatostatin receptors, which can be targeted with specific agonists [77, 78]. The D2-receptor agonist cabergoline, at doses of 0·5–7 mg/week, induces long-term biochemical remission in about 30% of patients [18, 79, 80]. Table 6 summarizes the most important drugs used for Cushing syndrome.

Table 6: **Summary of drugs for Cushing's syndrome** [84].

Drug	Dose	Main side-effects
Pituitary tumor-directed drugs		
Pasireotide	750–2400 µg per day subcutaneously injected	Hyperglycaemia, gastrointestinal complaints, and gall stones
Cabergoline	Up to 7 mg per week orally	Gastrointestinal complaints, dizziness, headache, and possible risk of cardiac valvulopathy
Retinoic acid	10–80 mg per day orally	Arthralgia, dryness of mouth and conjunctiva, headache, and gastrointestinal complaints
Steroidogenesis inhibitors		
Metyrapone	0·5–4·5 g per day orally	Gastrointestinal complaints, rash, hirsutism, hypertension, and hypokalaemia
Ketoconazole	400–1600 mg per day orally	Gastrointestinal complaints, gynaecomastia, hypogonadism, hepatotoxicity
Mitotane	3–5 g per day orally	Gastrointestinal complaints, gynaecomastia, hepatotoxicity, hypercholesterolaemia, adrenal insufficiency, and neurotoxicity
Etomidate	0·1–0·3 mg/kg/h intravenously	Gastrointestinal complaints, myoclonus, and pain at injection site
LCI699	4–100 mg per day orally	Gastrointestinal complaints, fatigue, headache, dizziness, arthralgia, and hypokalaemia
Glucocorticoid receptor antagonists		
Mifepristone	300–1200 mg per day orally	Clinical adrenal insufficiency, endometrial hyperplasia, hypertension, oedema, and hypokalaemia

Radiotherapy

Pituitary radiotherapy is a good primary therapy for nonsurgical candidates and is a second-line approach for persistent or recurrent disease after TSS, particularly when the tumor is invasive

and not surgically resectable [70, 71, 73]. Hypopituitarism is common after radiosurgery, whereas cranial nerve damage is rare [81].

Bilateral adrenalectomy

Bilateral adrenalectomy is the definitive treatment for Cushing's syndrome when rapid eucortisolism is necessary or when other therapies have failed [82]. Candidates for this treatment might include premenopausal woman who desire pregnancy soon after correction of Cushing's syndrome. Laparoscopic adrenalectomy has decreased the morbidity of this procedure [82]. Patients who undergo adrenalectomy need life-long glucocorticoid and mineralocorticoid replacement and individuals must be educated to avoid acute adrenal insufficiency episodes. Some investigators use plasma ACTH concentrations of more than 500 pg/mL (100 pmol/L) with hyperpigmentation as criteria for Nelson's syndrome diagnosis [83].

Nelson's syndrome

It is defined by the association of a pituitary macroadenoma and high ACTH secretion after adrenalectomy. Adrenalectomy is a radical therapeutic option to control persistent hypercortisolism in some patients with CD. This treatment is uncommonly (10–40%) followed by the development of Nelson's syndrome (NS) when the autonomous pituitary receives inadequate glucocorticoid feedback from exogenous steroid replacement [85]. The clinical manifestations of Nelson's syndrome include hyperpigmentation, in addition to signs and symptoms related to the growth of the tumor (i.e. headaches and visual symptoms). Such tumors can be very invasive, extending into surrounding structures such as cavernous sinuses. Apoplexy can also be one of the presentations of such tumors [86].

Today, NS is revisited with new criteria using more sensitive diagnostic tools evaluating the corticotroph tumor progression after adrenalectomy rather than to diagnose the NS [87].

b. Hyposecretion (Adrenocorticotropin deficiency)

Deficiency of corticotropin results in secondary hypoadrenalism and is the most serious of anterior pituitary hormone deficits [35]. During an intercurrent illness, an adrenal crisis with severe hyponatremia and hypovolemic shock may develop and can result in death if not diagnosed and treated appropriately. Patients who have hypopituitarism are protected somewhat from developing severe, acute hypoadrenalism compared with patients who have primary adrenal failure, as the angiotensin-aldosterone axis remains intact. Decompensation and shock occur during periods of illness or physical stress, such as surgery. Other symptoms of cortisol deficiency include lethargy, fatigue, weight loss, and nonspecific abdominal pain [35]. Hypoglycemia may be present, causing feelings of hunger, light-headedness, and sweating. Patients also may have hypotension and complain of postural symptoms. The pigmentation associated with primary adrenal failure is not present in patients who have corticotropin deficiency; the skin may be pale with an alabaster-like appearance [88].

4. Abnormalities of Thyrotropin Secretion

a. TSH-secreting pituitary adenoma:

Hyperthyroidism due to TSH-secreting pituitary adenoma (TSHoma) is a very rare disorder. It may be secondary to two different clinical situations, these are, TSHomas and resistance to thyroid hormone action (RTH). The main difference between these two syndromes consists in the presence of signs and symptoms of hyperthyroidism in patients with TSHoma, while RTH patients are in general euthyroid. Both TSHomas and RTH are characterised by elevated, circulating, free, thyroid hormone levels in the presence of measurable (normal or high) serum

TSH concentrations. Currently, it is proposed to classify these entities as 'central hyperthyroidism' [89].

Clinical features

When the diagnosis of central hyperthyroidism has been made, the differential diagnosis between TSHoma and RTH is mandatory. Improper thyroid ablation or unnecessary pituitary surgeries in patients with RTH are the distressing consequences of the failure to recognize these different disorders [90].

The signs and symptoms of hyperthyroidism are frequently associated in patients with TSHoma with those due to the compression of the surrounding anatomical structures, thus causing visual field defects, loss of vision, headache and partial or complete hypopituitarism. Patients are frequently misdiagnosed as Graves' disease, and some had inappropriate thyroidectomy or radio-iodine thyroid ablation. The occurrence of invasive macroadenomas is particularly high among patients with previous thyroid ablation by surgery or radio-iodine [91]. This aggressive transformation of the tumor resembles that occurring in Nelson's syndrome after adrenalectomy for Cushing's disease [89].

The clinical appearance of hyperthyroidism may be mild, sometimes overshadowed by signs and symptoms of concomitant acromegaly, or by neurological symptoms (headache, visual field defect) due to compression on the surrounding anatomical structures by the pituitary tumor [89].

Disorders of the gonadal axis are frequent, menstrual disorders being present in all females with mixed TSH/PRL tumors and in one-third of those with pure TSHoma. Central hypogonadism, delayed puberty and decreased libido were also found in a number of males with TSHomas and mixed TSH/FSH adenomas.

Laboratory Diagnosis

Nowadays, serum TSH is routinely measured by ultra-sensitive immunometric assays and circulating free thyroid hormones by direct immunoassays, a fact that greatly improved the diagnostic workup of hyperthyroid patients. As a consequence, central hyperthyroidism is now more often diagnosed earlier [90].

Treatment

The approach to TSHomas is trans-sphenoidal or subfrontal depending on the tumor volume and its suprasellar extension and invasiveness. The primary objectives are the removal of the pituitary tumor and the restoration of euthyroidism [89].

The operation may be difficult as the tumor may present a marked fibrosis [92]. Some adenomas are hard enough to be called 'pituitary stones' [93]. In addition, these tumors may be locally invasive, involving the cavernous sinus, internal carotid artery or other structures, thus rendering complete resection of the tumor either impractical or dangerous. In almost all patients with mixed TSH/GH hypersecretion, signs and symptoms of acromegaly concomitantly disappear. If surgery is contraindicated, pituitary radiotherapy should be considered [89].

Anti-thyroid drugs (methimazole 20–30 mg per day or propylthiouracil 200–300 mg per day) or somatostatin analogues, such as octreotide (100 mg s.c., b.i.d. or t.i.d.), along with propranolol (80–120 mg per day orally) can be administered in order to restore euthyroidism before surgery. However, this approach may cause TSH secretion from normal thyrotropes to be re-activated, so that one may lose a useful parameter to judge the complete removal of the adenoma, that is, the unmeasurable levels of circulating TSH few days after successful surgery [94].

The medical treatment of TSHomas today rests on long-acting somatostatin analogues, such as octreotide LAR or lanreotide SR or lanreotide Autogel [91, 95].

b. Thyrotropin deficiency

The symptoms and signs associated with thyrotropin deficiency are similar to those of primary hypothyroidism but usually are less severe, as there often is some residual thyrotropin secretion. With the exception of traumatic brain injury (TBI), thyrotropin deficiency usually occurs late in the evolution of hypopituitarism and often is seen with other anterior pituitary hormone deficits. In children, secondary hypothyroidism contributes to poor growth, delayed bone age, and failure of secondary dentition [35]. A permanent postoperative central hypothyroidism may also occur. Thus, transient or permanent T4 replacement therapy may be necessary [89].

5. Abnormalities of Gonadotropin Secretion

a. Gonadotroph pituitary adenomas

The majority of these tumors, previously labeled as non-functional, were indeed secreting follicle-stimulating hormone (FSH) or luteinizing hormone (LH), or both, or their respective alpha and beta subunits. However, hormone secretion by these tumors is minimal or inefficient and the clinical behavior is that of an inactive tumor [96, 97]. Gonadotroph adenomas account for 10–15% of all pituitary adenomas, whereas 5– 10% of all tumors are truly non-functional and are referred to as null-cell adenomas.

Clinical and biochemical characteristics

The accurate classification of non-functioning adenomas as gonadotroph tumors is necessary, as this might affect future medical treatments of recurrent or residual tumors. By the time most of these tumors are clinically recognized, they are large (>10 mm) and often have extension beyond the sella tursica. The most common clinical presentation has been related to the mechanical effects of the expanding macroadenoma with various signs and symptoms of hypopituitarism [86].

Hormone-related symptoms are rare. Cooper et al. have recently reviewed the clinical characteristics of 24 patients with symptomatic FSH hypersecretion reported in the literature. All were premenopausal women with a mean age of 32 years. Patients presented with ovarian hyperstimulation syndrome, consisting of menstrual irregularities, abdominal pain and evidence of enlarged ovaries. Most tumors were macroadenomas. Tumoral FSH hypersecretion in men may rarely manifest with testicular enlargement. Patients with symptomatic tumoral LH hypersecretion are also rare and have manifested as precocious puberty. Male patients present with increased serum testosterone concentrations and increased libido [86].

Treatment of gonadotroph adenomas

Surgery

The primary treatment for gonadotroph adenomas is transsphenoidal surgical adenomectomy.

Medical therapy

Currently, there is no standard medical therapy for gonadotroph adenomas. Dopamine agonists can suppress the release of gonadotropins and their subunits from the majority of gonadotroph tumors but is occasionally accompanied by improvement in visual field defects or tumor shrinkage. Dopamine agonist therapy should be tried when surgical resection is incomplete [86]. Therapy with GnRH agonists has, in general, been disappointing. The discordant effects of the drug on tumor growth and serum hormone concentrations were postulated to be caused by the

presence of factors other than GnRH controlling tumor growth [98]. Octreotide has been demonstrated to inhibit gonadotropin or aSU secretion. Its influence on tumor growth is less predictable and less common as minimal reductions in size were reported in fewer than 10–15% of treated patients. It cannot be recommended for routine use [99].

In summary, at present, there is no effective medical treatment for gonadotroph-secreting tumors, and thus the management does not differ from null-cell adenomas.

Radiation therapy

Radiation therapy can be used in patients whose adenomas could not be removed completely at surgery, or those with recurrent tumors that are not compressing the optic chiasm. It is not common practice to use adjuvant irradiation in completely resected tumors [100].

b. *Gonadotropin deficiency*

The clinical features of gonadotropin deficiency are determined by the gender and age at which the condition develops. Male infants with congenital hypogonadotropic hypogonadism may have a combination of unilateral or bilateral cryptorchidism and a microphallus caused by the relative androgen deficiency that occurs during the third trimester. Later, in adolescence, pubertal development can fail to progress normally. Gonadotropin deficiency in girls usually manifests in teenage years with delayed breast development and primary amenorrhea [35].

When gonadotropin deficiency is present in isolation, growth is normal during childhood and slow during adolescence when the growth spurt fails to occur. Despite this, the epiphyses fail to fuse at the usual age and the long bones continue to grow, ultimately resulting in tall stature and a eunuchoid habitus.

Because the symptoms of hypogonadotropism in men are nonspecific, they may not become evident for many years, particularly if fertility is not an issue. Adult men who acquire gonadotropin deficiency may notice a slowing of beard growth. Body hair may be lost, and if the hypogonadotropism is severe and prolonged, the skin becomes thin and fine wrinkles develop. Libido may be reduced and the ability to achieve and maintain an erection may be compromised. Azoospermia usually is present in prolonged gonadotropin deficiency. Testosterone deficiency can lead to nonspecific symptoms, such as tiredness, reduced muscle bulk, and reduced exercise capacity [35].

Conversely, in women, secondary gonadotropin deficiency often is diagnosed quickly when oligomenorrhea or amenorhea develops. In addition, women report symptoms of estrogen deficiency: vaginal dryness, dyspareunia, hot flashes, and breast atrophy. Pubic and axillary hair remains unless there is coexistant corticotropin deficiency with adrenal androgen deficiency [35].

B- Posterior Pituitary

The posterior pituitary is responsible for the secretion of oxytocin and vasopressin, also known as antidiuretic hormone (ADH). These hormones are important primarily for the regulation of parturition and water balance respectively [35].

ADH is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. Plasma osmolarity is the primarily stimulus for ADH secretion; however, other factors such as left atrial distention, circulating blood volume, exercise, and certain emotional states can also alter ADH release. ADH is considerably more sensitive to small changes in osmolarity than to similar changes in blood volume. ADH binds to vasopressin (V_2) receptors on the renal collecting ducts, which increases their permeability to water. This results in a significant increase in water reabsorption. Additionally, ADH increases blood pressure by increasing systemic vascular

resistance. The effect of ADH on blood pressure is mild in health, but becomes much more important in hypovolemic shock. It is used therapeutically as a vasopressor [9].

Oxytocin is also synthesized in the supraoptic and paraventricular nuclei of the hypothalamus. The principal physiologic functions of oxytocin are to stimulate cervical dilation and uterine contraction during labor and to allow milk to be let down into the subareolar sinuses during lactation. Oxytocin is one of the few hormones involved in a positive feedback loop. For example, uterine contractions stimulate oxytocin release from the posterior pituitary, which in turn increases uterine contractions.

6. Abnormalities of ADH

a. Diabetes Insipidus

Pituitary diabetes insipidus is most commonly associated with pituitary surgery and is most often transient [6]. Central DI (CDI) is characterized by polyuria, polydipsia, urinary frequency and nocturia. CDI usually has a sudden onset, due to the fact that urine can be concentrated up until 80-90% of ADH secreting cell are destroyed, after which urine can no longer be effectively concentrated and CDI becomes apparent [101]. For unknown reasons, patients with CDI report craving for ice water, and that ice water quenches their thirst better. Diminished ADH, and hence a decreased effect on prostaglandins and bone production, is a possible reason for the osteopenia associated with CDI [102].

Table 7. Diabetes Insipidus (DI) and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) [6].

	DI	SIADH
Associated conditions	1. Pituitary surgery 2. TBI 3. SAH (especially secondary to anterior communicating artery aneurysm)	1. Neurologic disease (SAH, TBI) 2. Neoplasia (especially non–small cell lung cancer) 3. Nonneoplastic lung disease 4. Drugs (carbamazepine)
Presentation	Polyuria	Hyponatremia
Plasma volume in awake patients	Euvolemic (practically speaking) Hypovolemic if not allowed access to fluids or unconscious	Euvolemic (or slightly hypervolemic)
Serum osmolarity	Hypertonic (>310 mOsm/L)	Hypotonic (<275 mOsm/L)
Serum Na+	Rising (>145 mEq/L)	Falling (<135 mEq/L)
Urine volume	Voluminous (4 to 18 L/day)	Low (but not normally absent)
Urine osmolarity	Relatively low (<200 mOsm/L)	Relatively high (>100 mOsm/L)
Urinary Na+	Normal (or variable)	>30 mEq/L
Treatment	Supportive DDAVP	Fluid restriction If Na^+ < 120 mEq/L consider hypertonic saline to correct sodium (but no faster than 1 mEq/L/h) Intravenous urea Demeclocycline Lithium (rarely used)

DDAVP, Desmopressin (1-desamino-8-D-arginine vasopressin); DI, diabetes insipidus; SAH, subarachnoid hemorrhage; SIADH, syndrome of inappropriate diuretic hormone; TBI, traumatic brain injury.

The preferred replacement therapy for treating CDI is DDAVP (Minirin). It can be given as an intranasal spray, oral tablet or lyophilisate (melt) form [103]. A possible side effect is hyponatremia, brought on by continued ingestion of fluids despite the resolution of the polyuria. By allowing the effects of DDAVP to dissipate before the next dose, the diuretic phase will not be missed and severe hyponatremia can be avoided [102].

Chlorpropamide (Diabinese) also reduces polyuria by up to 75% by acting on the renal tubule to respond more effectively to residual ADH and is also thought to cause release of ADH. Chlorpropamide is mainly used in patients with mild DI who need only modest reduction in urine output [102].

b. Syndrome of Inappropriate Antidiuretic Hormone

Oversecretion or "inappropriately high" levels of ADH (or ADH-like hormones) results in the syndrome of inappropriate ADH (SIADH). SIADH is most commonly associated with central nervous system injury or trauma as well as certain cancers, especially lung cancer. SIADH typically presents with the signs and symptoms of hyponatremia. Characteristics of DI and SIADH are summarized in Table 7.

Hypopituitarism

The term, hypopituitarism, describes the deficiency of one or more of the hormones of the anterior or posterior pituitary gland. Panhypopituitarism often is used in clinical practice to describe patients deficient in GH, gonadotropins, corticotropin, and thyrotropin in whom posterior pituitary function remains intact [35].

Hypopituitarism is a rare condition with a prevalence rate of 45.5 per 100,000 [104]. There are many identified causes of hypopituitarism, but recent recognition that other conditions, such as head injury and cranial radiotherapy, can cause hypopituitarism will result in more cases being diagnosed and, consequently, an increase in prevalence. The clinical impact of hypopituitarism can be variable and is determined by the age at which the condition occurs, its rapidity of onset, the gender of the patient, the underlying cause, and the pattern of hormone deficiencies.

Table 8: Causes of hypopituitarism:

1. Congenital hypopituitarism.
2. Pituitary tumors.
3. Suprasellar masses [12]:-

▪ Craniopharyngiomas	▪ hamartoma
▪ Rathke's cleft cyst;	▪ meningioma; and
▪ dermoid,	▪ suprasellar aneurysm.
▪ epidermoid,	▪ astrocytomas,
▪ arachnoid cysts;	▪ optic nerve gliomas
▪ germinoma;	▪ metastatic disease

4. Radiation
5. Traumatic brain injury
6. Infiltration by [105]:-

▪ Lymphocytic hypophysitis	▪ Wegener's granulomatosis,
▪ sarcoidosis,	▪ Langerhans' cell histiocytosis
▪ tuberculosis,	▪ syphyllis

Clinical features of hypopituitarism

The general features of hypopituitarism are nonspecific and often evolve insidiously before a diagnosis is made, resulting from the local effects of the underlying pathology or the developing endocrinopathy. Deficits of anterior pituitary hormones may be secondary to hormone excess caused by functional pituitary tumors, for example, suppression of gonadotropins in hyperprolactinemia or GH deficiency caused by cortisol excess in Cushing's syndrome [106]. In these situations, the deficits may recover when the underlying endocrinopathy is treated. Nonspecific symptoms include a feeling of general ill health, being abnormally tired, increased lethargy, feeling cold, weight loss, reduced appetite, and abdominal pain. Symptoms attributed to the local effects of any underlying tumor include headaches, visual disturbance (typically a bitemporal hemianopia), or cerebrospinal fluid rhinorrhea [35].

Pituitary incidentaloma

The pituitary incidentaloma (PI) is a lesion in the pituitary gland found by either CT or MRI evaluation of the brain for an unrelated indication, in a patient without overt signs or symptoms

of pituitary disease [107]. Although pituitary incidentalomas are not functional by definition, this term should not be used interchangeably with clinically non-functional pituitary adenomas (CNFPAs), since the latter usually present with mass effect [108]. Incidentally discovered pituitary adenomas represented about 12% of the pituitary tumors, [109] and about 4-20% of healthy volunteers [110].

Pathologic examination of resected tissue confirms the diagnosis of silent functioning adenomas and determines the final classification of these tumors as silent subtype 3, prolactinomas, gonadotroph adenomas, silent corticotroph adenomas, or silent somatotroph adenomas. Each class of silent adenomas has a unique diagnostic and ultrastructural profile, reflective of the cell of origin. Knowledge of the subtypes may help determine postoperative surveillance as some of these adenomas exhibit more aggressive growth.

Clinical features

Pituitary incidentalomas are mostly asymptomatic. Most are microincidentalomas but endocrinologists may see a larger portion of patients with macroincidentalomas referred to them for further evaluation [107]. The initial approach to a patient with pituitary incidentaloma should be directed to the mass effect and the hormonal activity.

Hormonal screening

The 2010 Endocrine Society guidelines recommend screening patients with a PRL and IGF-1 measurement if diagnosed with a pituitary incidentaloma. Detecting a prolactinoma would alter management of the incidentaloma, and early detection of acromegaly may prevent later comorbidities. However, screening for Cushing disease is reserved for those with clinical suspicion. Plasma ACTH levels are not recommended as a screening measurement for silent corticotroph adenomas [1, 39].

Treatment of pituitary incidentalomas

Most microincidentalomas can be followed conservatively unless there is evidence for mass effect. Macroincidentalomas should be followed for life [107]. Knowledge of PRL positive staining may potentially provide an option for dopamine agonists in treatment of recurrent silent prolactinomas [111].

Pituitary apoplexy

Apoplexy is a hemorrhagic infarction of the tumor that manifests clinically as sudden onset of severe headache, nausea/vomiting, vision loss and cranial nerve palsies. If unrecognized and untreated, these patients may suffer from hypotension and shock secondary to adrenal insufficiency as well as irreversible vision loss or diplopia [107].

Surgical intervention is generally recommended in cases with progressive vision loss or cranial neuropathy, preferably within 24–48 h of onset if feasible. While most cases of pituitary apoplexy are spontaneous, precipitating factors may include head injury, anticoagulant therapy, dopamine agonists, radiation therapy, or dynamic endocrine tests [112]. Clinically significant pituitary apoplexy is a rare event in patients with pituitary microadenomas [113].

In the study by Arita et al, the risk of pituitary apoplexy during 5 years follow up was 9.5% and all such tumors were macroadenomas [114]. In a recently published meta-analysis of 11 studies with a median follow up of 3.9 years looking at the natural history of pituitary incidentalomas and non-functional pituitary macroadenomas, the authors found a trend for greater incidence of pituitary apoplexy in macroadenomas (1.1 per 100 PYs) compared to microadenomas (0.4 per 100 PYs) that did not reach statistical significance [115].

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