

A Review of Pituitary Gland for General Physicians

Tamer Shalaby Boutrus*

Abstract

Abnormalities of the pituitary gland are common; general physicians should be confident in managing pituitary gland disorders like panhypopituitarism which is deficiency of hormones secreted by the pituitary gland and can be life threatening, hypersecretion of pituitary hormones which can lead to multiple comorbidities, and diagnosing pituitary adenomas which may have mass effect and serious consequences. This publication is a general approach to anatomy, physiology, and pathology of pituitary gland to aid diagnosis and management of common presentations related to pituitary gland disorders through literature review.

Keywords: Pituitary adenoma; Pituitary hormones; Panhypopituitarism; IGF-1; Acromegaly; Growth hormone prolactinoma; Gonadotrophins; ACTH; Cushing disease; TSH.

Introduction

The pituitary gland is surrounded by the optic chiasm superiorly, cavernous sinus bilaterally which includes internal carotid arteries, cranial nerves 3,4,6, and two of the branches of the fifth cranial nerve (V_1/V_2), and sphenoid sinus below. The pituitary gland has two lobes, anterior lobe constitutes eighty percent of the gland and secretes six hormones which are the Growth, Prolactin, Thyroid-stimulating, Adrenocorticotrophin, Follicle-stimulating, and Luteinizing hormones.

While the posterior lobe releases vasopressin (antidiuretic) and oxytocin hormones

through nerve cells activated by the hypothalamus. The anterior lobe is known as adenohypophysis and is derived from the oral ectoderm and is epithelial in origin, while the posterior lobe which is known as neurohypophysis is formed from the neural ectoderm [1].

Anatomy and embryology of pituitary gland

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¹Consultant Physician, MBBCh, Diploma in Diabetes and Endocrine (UK), MSC, FRCP(Lon), Galway Clinic Hospital, Republic of Ireland

***Corresponding Author:** Tamer Shalaby Boutrus, Consultant Physician, MBBCh, Diploma in Diabetes and Endocrine (UK), MSC, FRCP(Lon), Galway Clinic Hospital, Republic of Ireland.

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Rathke's pouch arise from the thickening of oral ectoderm (nasopharynx), which is an upward evagination extends towards the neural ectoderm, this process starts at week four, at the same time a downward extension of the diencephalon forms the posterior lobe, and both connect to form the pituitary gland. Rathke's pouch separates from the oral ectoderm between week six to eight when the anterior wall proliferates to perform the anterior lobe while the posterior wall of the pouch forms the intermediate portion of the gland. The anterior lobe differentiates into five specialized endocrine cell types (Somatotrophs, Corticotrophs, Lactotrophs, Gonadotrophs, and Thyrotrophs) [2].

Understanding the anatomy can explain some clinical presentations of large pituitary macroadenoma like bitemporal hemianopsia or quadrantanopias due to optic chiasm compression, or diplopia due to cavernous sinus infiltration. Understanding the embryology can explain many mutations

leading to tumours or hormonal deficiency, like Rathke's cleft cysts which is a common derivative from Rathke's pouch remnants and is usually asymptomatic, however, can present with hypopituitarism and headache due to hydrocephalus [3].

The blood supply of the anterior pituitary gland is under low pressure via the superior hypophyseal artery which originates from the posterior communicating or internal carotid arteries, while the posterior lobe has a high-pressure blood supply from the inferior hypophyseal artery which originates from the meningohypophyseal trunk [4].

This difference in pressure between the blood supply of the two lobes explains why the anterior lobe is more susceptible to ischemia in Sheehan's syndrome compared to the posterior lobe which is usually spared [5].

Differential diagnosis of sellar mass

Pituitary adenomas (microadenoma if less than 1 cm or macroadenoma if 1 cm or more) are common causes of Sellar masses. Other causes are primary or metastatic tumours, cysts, physiological enlargement (in pregnancy), or lymphocytic hypophysitis [6]. Adenomas may be functioning causing hypersecretion of hormones or nonfunctioning causing mass effect leading to hormone deficiency from compression on the rest of pituitary tissue [7].

Gonadotroph and thyrotrope adenomas are mainly nonfunctioning and rarely cause hormonal hypersecretion, while corticotrope adenomas usually cause Cushing disease, lactotroph adenomas usually cause hyperprolactinemia, and somatotroph adenomas cause acromegaly. Often lactotroph and somatotroph adenomas

simultaneously secrete both prolactin and growth hormone in excess [8].

Physiological hyperplasia of pituitary gland can present as a Sellar mass, common causes are hyperplasia of lactotroph secondary to pregnancy and hyperplasia of thyrotrope and gonadotroph after prolonged period of primary hypothyroidism and hypogonadism respectively [9]. Craniopharyngiomas are benign nonfunctioning tumour which arise from remnants of Rathke's pouch, they can cause mass effect, hypopituitarism, and

central diabetes insipidus. While meningioma is another benign tumour which can also cause hypopituitarism and visual impairment if arises near the Sella. Lymphoma can affect pituitary and hypothalamus, and all can locally invade the extrasellar space [10]. Up to 2% of Sellar masses can be due to a metastatic disease, common primaries are breast and lung cancers [11]. Several types of cysts can cause Sellar mass like arachnoid, dermoid, and Rathke's cleft cysts [12].

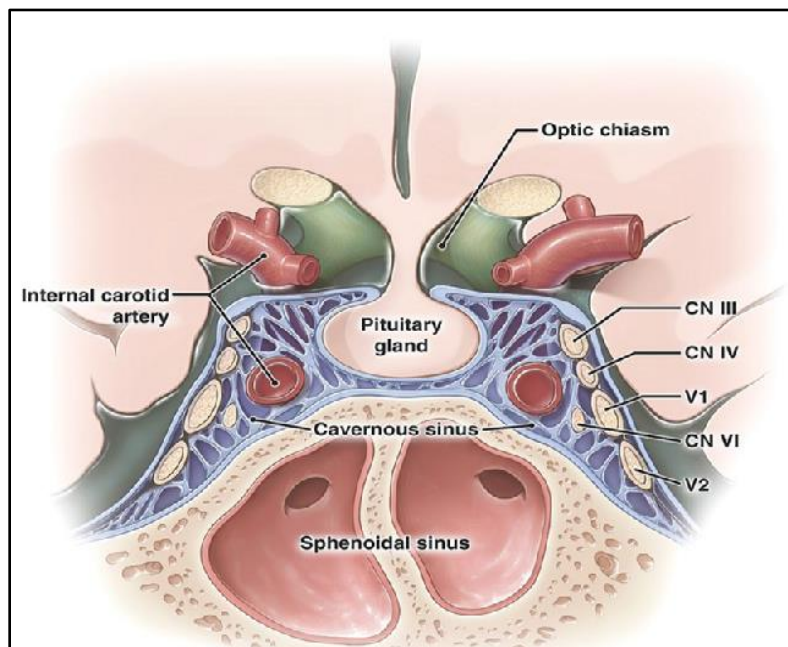


Figure 1: Pituitary gland is surrounded by the optic chiasm superiorly, cavernous sinus bilaterally which includes internal carotid arteries, cranial nerves 3,4,6, and two of the branches of the fifth cranial nerve (V₁/V₂), and sphenoid sinus below.

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and finally lymphocytic hypophysitis can cause Sellar mass due to lymphocytic infiltration of the pituitary gland which usually occurs in women in late pregnancy or postpartum period and after treatment with immune check point inhibitors. [13,14]. Indication for surgery includes mass effect compressing the optic chiasm or leading to hypopituitarism, malignant tumour, or adenomas causing hypersecretion of hormones except prolactinoma where medical therapy with dopamine agonist can lead to shrinkage of the macroadenoma. [15]. Pituitary tumours can affect visual fields in different ways, when tumour involves one side of the optic chiasm, or an optic nerve presents with superior temporal quadrantanopia or monocular field defect. Pituitary apoplexy can present with sudden onset monocular visual loss [16]. Tumours compressing the centre of the optic chiasm above it usually presents with bitemporal hemianopia, initially the superior temporal fields are lost as the tumour compresses the chiasm from below then inferior temporal visual field loss occurs as the tumour progress [17]. Rarely, tumours can compress the optic tract leading to homonymous hemianopsia and relative afferent pupillary defect.

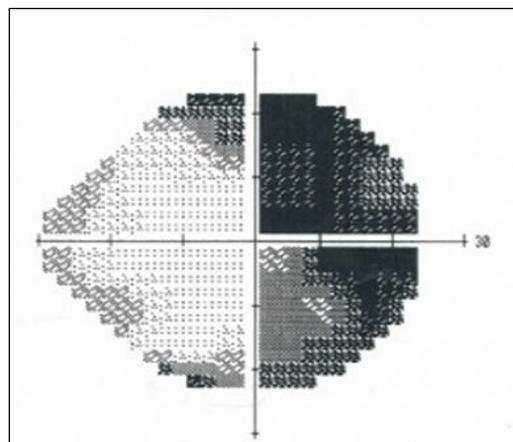


Figure 2: Temporal visual loss in right eye.

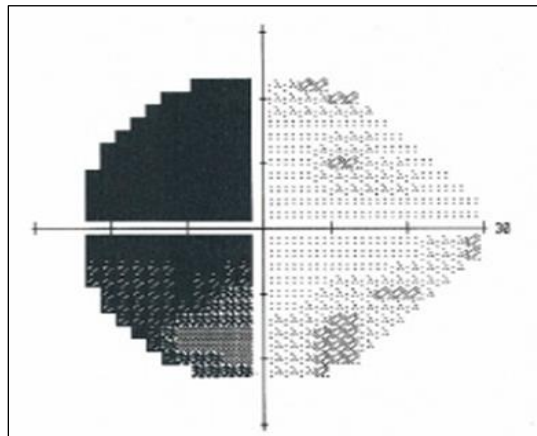


Figure 3: Temporal visual loss in left eye.

Bitemporal hemianopia on examination

Unlike functioning pituitary adenomas, the nonfunctioning adenomas are usually diagnosed late when large enough to cause symptoms related to mass effect including headache and visual symptoms like bitemporal hemianopia. Although nonfunctioning pituitary adenomas do not oversecrete hormones, they can compress the pituitary tissue leading to deficiency of hormones with associated clinical features, often cases of nonfunctioning pituitary tumours are diagnosed incidentally [18].

The suprasellar extension of the adenoma leads to pressure effect on the optic chiasm as mentioned above, which causes visual field loss like superior temporal quadrantanopia early or bitemporal hemianopsia, less commonly, diplopia due to 3rd cranial nerve compression can occur. Headache which is usually diffuse occurs but less frequent than visual field defects as it requires more Sellar expansion before presentation [18]. Pituitary apoplexy which presents with thunderclap headache, cortisol deficiency, and visual impairment (field and/or diplopia) occurs due to haemorrhage in pituitary

macroadenoma can occur rarely and spontaneous cerebrospinal fluid leak can complicate pituitary tumours [19].

Studies showed that between 10% of Sellar lesions were incidental pituitary lesions discovered on magnetic resonance imaging (MRI) requested for other indications, more than 60% of these incidental pituitary adenomas were macroadenomas (more than 1 cm) [18]. Pituitary hormone deficiencies can occur in nonfunction pituitary macroadenoma as mentioned above due to compression on the pituitary tissue, secondary hypogonadism (low/inadequate normal FSH/LH in presence of low testosterone/oestradiol) leading to low libido in both sexes, erectile dysfunction or amenorrhoea in males and females respectively [20]. and Growth hormone (GH) deficiencies are usually affected early, ACTH, and TSH deficiencies can occur but less common than gonadotrophin and GH deficiencies [18].

Hyperprolactinemia up to 200 ng/mL can occur in nonfunctional macroadenoma due to the compression of the pituitary stalk, this compression prevents the hypothalamic

influence from inhibiting prolactin secretion [21].

Diagnosis of nonfunctioning pituitary macroadenomas

Thorough history of symptoms of hypopituitarism especially gonadotropin deficiency (fatigue, low libido, amenorrhoea, or erectile dysfunction) and inquiry on visual impairment or presence of new but chronic diffuse headache. Blood tests, basic ones like full blood count, renal profile, and glucose levels plus full pituitary profile including 8 am ACTH/cortisol, FSH, LH, testosterone or oestradiol, prolactin, IGF-1, and TSH with free T₄. Alpha subunit levels (raised in cases of gonadotroph adenomas). DEXA scan if secondary hypogonadism is confirmed. MRI pituitary with and without contrast to assess for a Sellar mass and its local mass effect on surroundings, and a formal visual field and acuity testing [22].

Physiology of pituitary hormones

Six hormones are secreted from the anterior lobe of the pituitary, GH is secreted by the somatotrophic cells of the anterior pituitary gland which is under the influence of the hypothalamus via growth hormone-releasing hormone (GHRH) and growth hormone-inhibiting hormone (GHIH) [23].

Prolactin is secreted by lactotroph cells and is inhibited by dopamine and stimulated by thyrotropin-releasing hormone (TRH), medications like dopamine antagonist (antipsychotics and antiemetics), suckling, stress, pregnancy, oestrogen, and sleep [24].

Gonadotrophins are follicular stimulating and luteinizing hormones (FSH, LH) secreted by the gonadotropin cells and contain a similar alpha chain and a different beta chain. Gonadotropin-releasing hormone (GNRH)

from the hypothalamus increases the secretion of FSH and LH [25].

Adrenocorticotrophic hormone (ACTH) is secreted by corticotrophic cells under the influence of corticotropin-releasing hormone (CRH) from the hypothalamus and inhibited by a negative feedback from cortisol, While the last hormone secreted by the anterior pituitary lobe is the thyroid-stimulating hormone (TSH) which is secreted by thyrotropes and is formed of an alpha chain and one beta chain, secretion is increased by the thyroid-releasing hormone (TRH) from the hypothalamus and inhibited by Free T₄ negative feedback [26]. Two hormones secreted by the posterior pituitary gland, vasopressin which is the antidiuretic hormone (ADH) and oxytocin. Both are packaged in secretory granules at the hypothalamus and move down the axon to be stored at the posterior pituitary lobe. ADH controls serum osmolality and increases with serum hyperosmolality or volume loss and levels of ADH are reduced with hyperosmolality.

Function of the pituitary hormones

GH is an anabolic hormone which induces growth of tissues and organs, reduces apoptosis, increases uptake of amino acids, and enhances cellular proliferation. GH produces insulin-like growth factor-1 (IGF-1) enhancing glycolysis (break down of glycogen in liver to glucose) and stimulating lipolysis (break down of fat) leading to increase in energy levels [23].

Prolactin stimulates the development of breast tissue and enhance milk production, FSH stimulates the development of sperms in males and ova in females while LH triggers ovulation in women while in males it

stimulates the release of testosterone from the Leydig cells of the testes. ACTH stimulates the production of cortisol and androgens (DHEA) with minimal effect on aldosterone from the adrenal gland. TSH induces the secretion of thyroid hormones thyroxine (T₄) which is converted to triiodothyronine (T₃) and in turn increases the basal metabolic rate resulting in heat production and enhance bone and central nervous system maturation [27].

ADH from the posterior lobe leads to increased reabsorption of water from the collecting ducts at the kidneys and induces vasoconstriction, the net effect is to keep the equilibrium of intracellular and extracellular osmolality. Oxytocin induces uterine contraction and the release of milk from the breast tissue in females, while in male's oxytocin stimulates contraction of the vas deferens to push the semen and sperm forward (ejaculation) [28].

Functional abnormalities in pituitary gland

Excess GH mainly due to a secreting adenoma leads to acromegaly in adults (after fusion of bone epiphysis) and is characterized by excess sweating, frontal bossing, prognathism, obstructive sleep apnoea, insulin resistance, and hypertension. Diagnosis is clinically and confirmed by an increase in IGF-1 levels, and treatment is mainly surgical although adjunct somatostatin analogues or radiotherapy can be used [29]. GH deficiency in adults is difficult to diagnose and usually presents with central adiposity, reduced muscle mass, osteopenia or osteoporosis, and fatigue [23]. Increased prolactin levels can be physiological and transient (pregnancy, sleep, exercise, stress, lactation, and sexual

intercourse) while pathological causes of hyperprolactinemia including medications can be symptomatic leading to hypogonadism (amenorrhoea in females or erectile dysfunction in males with loss of libido in both sexes), galactorrhoea, and osteoporosis, treatment is usually medical by using dopamine agonists like cabergoline [25].

Deficiency of prolactin is only significant in females when failure to lactate occurs after pituitary insult like in Sheehan's syndrome [24]. Increase in gonadotrophins can be related to loss of negative feedback from the gonads or rarely due to a pituitary adenoma. ACTH abnormalities can be related to adrenal or pituitary dysfunction or ectopic release from a tumour [30].

TSH levels are inversely proportional to T₄ levels in primary thyroid disease, while if the abnormality is in the pituitary, usually the TSH feedback is lost. Decreased levels of ADH due to an insult to the posterior lobe can lead to central diabetes insipidus (DI) which causes excess free water excretion in the urine, presenting with polyuria, polydipsia, and nocturia with raised osmolality in blood with abnormal low urinary osmolality. Excess ADH on the other side increases water retention and leads to hypervolemic hyponatremia. Common causes of increased ADH are intracranial or respiratory diseases, medications, pain, nausea, and malignancy. Finally, oxytocin insufficiency slows down uterine contractions and reduce milk ejection in females, while excess oxytocin leads to difficulty in maintaining pregnancy due to premature contraction of a hypertrophied uterus [28].

Causes of hypopituitarism

Hypopituitarism is a reduced secretion of pituitary hormones due to a disease in the pituitary or hypothalamus. Patients may be asymptomatic or complain of fatigue and other symptoms related to hormones deficient, patients with large Sellar mass can present with headache and visual impairment. Hypothalamic lesions can present with vasopressin (ADH) deficiency more commonly than pituitary lesions as some ADH is present in the neurons which terminate in the median eminence [31]. Causes of hypopituitarism are tumours (benign like craniopharyngioma or metastatic malignant tumours commonly from breast or lung), radiotherapy treatment to brain or nasopharynx can damage the pituitary gland [32].

Sarcoidosis and Langerhans cell histiocytosis can infiltrate pituitary or hypothalamus leading to hypopituitarism, while haemochromatosis usually affects the pituitary gland with reduction of gonadotrophins mainly that can be prevented by early phlebotomy. Infiltrative diseases can show thickening of the infundibulum on MRI [33]. Ischemic strokes and subarachnoid haemorrhage can rarely present with hypopituitarism, while meningitis can present with hypopituitarism more commonly in immunocompromised patients [34].

Severe traumatic brain injuries can present acutely with ADH deficiency which usually recovers, while deficiency of anterior pituitary hormones may occur few months later [35]. Hypopituitarism can improve or worsen after pituitary surgery and can occur years after pituitary radiotherapy [36,37]. Lymphocytic hypophysitis is the most common form of inflammation of the pituitary gland

(hypophysitis), usually idiopathic due to infiltration of the pituitary gland with lymphocytes leading to sellar mass on imaging and hypopituitarism due to destruction of pituitary gland. Lymphocytic hypophysitis is common in late pregnancy or postpartum period [38].

Hypophysitis due to check point inhibitors (mainly ipilimumab) can present with hypopituitarism and headache due to gland enlargement [39]. IgG4 associated hypophysitis due to infiltration with plasma cells which usually affect other organs like pancreas [40]. Sheehan syndrome is infarction of the pituitary gland secondary to significant postpartum haemorrhage and is quite common worldwide, initial presentation is failure to lactate or resume menses, then significant hypotension, fatigue occur due to panhypopituitarism. [41]. Pituitary apoplexy occurs due to bleeding into a macroadenoma, apoplexy as mentioned before presents with thunderclap headache, diplopia, and hypopituitarism with acute life-threatening cortisol deficiency, treatment is urgent cortisol replacement plus crystalloids and urgent referral to neurosurgery if local mass effect causing visual impairment or neurological signs [42].

Congenital deficiencies and abscesses are quite rare causes of panhypopituitarism. Empty Sella syndrome is a radiological description when a large Sella turcica is not fully filled with pituitary tissue. Two types of empty Sella syndrome are recognized, secondary empty Sella is a term used when pituitary treatment was given leading to partial reduction in the pituitary gland which presents more commonly with hormonal deficiency, while in primary empty Sella the cerebrospinal fluid leaks to the Sella causing

enlargement and pressure in the pituitary gland from a defect in the diaphragm Sella, hypopituitarism is unlikely unless the leak is significant [43]. Clinical features of hypopituitarism depend on several factors including the number of hormones deficient, the rapidity and the severity of the deficiency.

Secondary adrenal insufficiency

(Low ACTH) can present with postural hypotension, fatigue, anorexia with weight loss, reduced libido, hypoglycaemia in mild cases, while severe deficiency can be life threatening in severe cases of cortisol deficiency due to vascular collapse as cortisol is a key hormone for optimum vascular tone. Contrary to primary adrenal insufficiency, ACTH deficiency doesn't affect aldosterone secretion significantly, therefore salt wasting, and hyperkalaemia are not prominent in secondary adrenal insufficiency, hyperpigmentation doesn't occur in secondary adrenal insufficiency contrary to primary adrenal insufficiency. Hyponatraemia is common in both causes of adrenal insufficiency due to excess ADH secretion [44].

Secondary hypothyroidism

(Low TSH) presents with dry skin, facial puffiness, fatigue, cold intolerance, bradycardia, slow reflexes, and constipation. Prolactin deficiency rarely occurs in isolation, the only clinical sign of prolactin deficiency is failure to lactate after delivery [45]. To assess for corticotropin deficiency, recommendations are basal ACTH level with 8 am cortisol level, a low cortisol level below 100 nmol/L in the presence of low or inadequately normal ACTH is strongly suggestive of secondary (or tertiary-hypothalamus) adrenal insufficiency. While ACTH level higher than normal range in the

presence of low cortisol is suggestive of primary adrenal insufficiency. If cortisol level at 8 am is over 400 nmol/L this is considered an adequate cortisol level which is likely sufficient when physical stress occurs. Recommendations for indeterminate 8 am cortisol levels (levels between 100-400 nmol/L) are to perform a provocative test called cosyntropin stimulation test (known as short synacthen test-SST) [46]. Administer 0.25 mg of cosyntropin (synthetic ACTH) IM or IV and check cortisol levels after 60 minutes, a cortisol level of more than 400 nmol/L or rise by more than 150 nmol/L is considered a normal response (healthy adrenal gland which can produce cortisol when stimulated), interpretation of a positive test is either a complete ACTH deficiency which has not been long enough to cause adrenal atrophy or partial ACTH deficiency [47]. To assess for thyrotropin (TSH) deficiency, TSH levels are checked with either free T₄ or total T₄ and T₃ uptake, low levels of T₄/T₃ with low or inadequately normal TSH is suggestive of secondary (or tertiary-hypothalamus) hypothyroidism [48].

Gonadotrophin deficiency in adults

Hypogonadism is a reduction in sperm count and/or testosterone levels (males) and amenorrhoea with reduction in oestrogen levels (females). Primary hypogonadism refers to testicular or ovarian pathology with raised levels of FSH and LH, while secondary hypogonadism refers to a disease in hypothalamic-pituitary axis leading to a deficiency in gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus with reduction in FSH/LH or inadequately normal levels from the pituitary gland. Common cause of secondary hypogonadism is mass lesion in pituitary gland leading to gonadotrophins and growth

hormones deficiencies mainly with preservation of more vital hormones like ACTH and TSH. Hyperprolactinemia is another common cause of secondary hypogonadism as it suppresses gonadotropin secretion [49].

Other acquired causes of secondary hypogonadism like causes of hypopituitarism. Few medications can cause secondary hypogonadism with prolonged use like administration of GnRH analogues (prostate cancer), androgens use in athletes, and chronic treatment with steroids or opioids [50,51]. Patients with chronic organ failure like renal or liver disease and acquired immune deficiency syndrome have coexisting secondary hypogonadism while those with any critical illness or anorexia nervosa can present with temporary secondary hypogonadism [52]. Total testosterone levels are lower in men with type 2 diabetes mellitus. Men with obesity have lower levels of total testosterone due to a reduction in sex hormone binding globulin (SHBG), however, secondary hypogonadism is common in patients with obesity as well and measuring the free testosterone and if low can point towards secondary hypogonadism with low or inadequately normal LH [53]. Sarcoidosis and Langerhans cell histiocytosis can lead to hypothalamic hypogonadism, while hemochromatosis leads to pituitary hypogonadism which can be reversed with phlebotomy if initiated early [54].

Growth hormone deficiency in adults

Causes of growth hormone (GH) deficiency like causes of hypopituitarism and includes tumours compressing the pituitary tissue, surgery or radiation to the pituitary gland, infiltration like sarcoidosis, haemorrhage in a

macroadenoma like in Sheehan syndrome, and finally idiopathic cases can occur in up to 8% of cases of GH deficiency [55].

Gonadotrophins and GH deficiencies are generally more likely to occur in pituitary disease than ACTH and TSH as mentioned above and should be monitored in presence of Sellar mass [56]. In adults GH deficiency results in a reduction in bone mineral density, lean body mass due to reduction in muscle mass, and reduction in quality of life as well as increase in central obesity, cardiovascular disease (CVD) and mortality [57]. Several studies suggest that CVD in GH deficiency is related to multiple factors like increase in inflammatory markers and endothelial dysfunction as well as dyslipidaemia with higher levels of LDL and lower levels of HD [58]. Diagnosis of GH deficiency depends on presence of pituitary disease and low levels of IGF-1 levels, if the levels are equivocal and the suspicion is high a GH provocative test is indicated. GH and IGF-1 levels tend to decrease with aging and in the absence of a clear pituitary or hypothalamic disease replacement is not indicated [59].

However, a low level of IGF-1 (depending on age and sex reference) in the presence of pituitary disease does confirm the diagnosis. Provocative test is indicated when the clinical suspicion for GH deficiency is high in presence of equivocal IGF-1 levels adjusted to age and sex, the standard tests are insulin induced hypoglycaemia which should raise the GH level and arginine with GHRH infusion which again should raise the GH levels in the absence of deficiency.

Recently, macimorelin (ghrelin receptor agonist) has been approved, a poor response (subnormal or no rise in GH) is considered a

confirmation of GH deficiency when IGF-1 levels are equivocal and pituitary disease present as explained above [60].

After confirming GH deficiency treatment with GH showed evidence of increase in muscle mass with reduction in body fat, improvement in cardiac function, and quality of life. However, effect on bone mineral density in females and mortality are controversial [61].

Should every patient with GH deficiency be treated?

Children with confirmed GH deficiency should be able to continue GH treatment in their adulthood, while adults who have confirmed new onset GH deficiency with symptoms like fatigue and lack of energy, a discussion of risk versus benefit should be initiated with a decision to treat or not accordingly. The rationale of this discussion that although GH treatment can improve muscle mass, reduce body fat, and possibly improves quality of life and cardiac function with an increase in bone mineral density in males but often there is no marked improvement in some patient's quality of life with no change in energy levels or reduction in mortality and few patients suffer from side effects from treatment like leg oedema, carpal tunnel syndrome, arthralgia, and insulin resistance [61].

Patients with malignancy should not be treated with GH replacement and as mentioned above, elderly patients with low levels of IGF-1 and in the absence of pituitary disease should not be offered the replacement therapy as no evidence of benefit with possibility of side effects.

Replacement can be given daily or weekly, daily recombinant human GH (rhGH) by

subcutaneous injection is given in the evening and initiated at lower dose then slow escalation of the dose aiming IGF-1 at mid-level of age-adjusted normal range over two months interval [62]. Somapacitan is an approved long-acting GH (attached to albumin) and is given weekly as a subcutaneous injection and showed similar effects to daily rhGH [63].

Treatment of hypopituitarism

Hormone replacement therapy for GH is unique (mentioned above) and prolactin replacement is not available, the replacement treatment of other hormones like ACTH, TSH, FSH, and LH is quite like the treatment used for primary deficiencies in target glands Hydrocortisone dose of 15-25 mg/day depending on weight and in divided doses to simulate cortisol natural pattern is recommended in patients with ACTH deficiency, higher doses are required in physical stress like infection with fever or illness [64].

It is important to assess for the appropriate dose for individual patients as inadequate dose of hydrocortisone can cause symptoms of cortisol deficiency like nausea, fatigue, and postural hypotension, while excess doses can lead to osteoporosis and insulin resistance. Like secondary hypothyroidism, ACTH cannot guide adequacy of hydrocortisone dose, also, checking cortisol levels may be not accurate due to fluctuating levels, experts suggest do judge the adequacy of the dose clinically [65]. Dehydroepiandrosterone (DHEA) replacement can benefit females psychologically in whom suffer combined ACTH and gonadotropin deficiency, while Fludrocortisone treatment is not indicated in secondary cortisol deficiency, the reason is

aldosterone release is controlled by Angiotensin II and potassium levels much more than ACTH [66].

Levothyroxine is used to replace low levels of free T₄ in patients with secondary hypothyroidism, it is essential to rule out cortisol deficiency prior to initiating levothyroxine replacement as it leads to increase of the little existing cortisol and can induce a crisis. Starting dose of levothyroxine replacement is 1.6 mcg/kg, TSH cannot be used as a marker of adequate levothyroxine replacement in secondary hypothyroidism and the aim of adequate replacement is upper half of the reference range of free T₄ [67].

Treatment of LH and FSH deficiency depends on the sex and desire for fertility.

Testosterone treatment is provided to males who do not desire fertility and the adequacy of treatment can be determined by normal levels of morning testosterone levels. Males or females who desire fertility are treated with gonadotropins if the pathology is in the pituitary gland or gonadotropin-releasing hormone (GnRH) if the pathology is in the hypothalamus. Females with hypogonadism who don't desire fertility can be offered oestradiol-progestin replacement therapy, transdermal oestradiol continuously with progestin (females who have uterus) on day 1 and 12 of each month [68].

Pituitary incidentalomas

A pituitary lesion discovered accidentally during brain imaging is called a pituitary incidentaloma (PI), the prevalence of PI accidentally discovered on MRI is common [69].

Majority of PI is nonfunctioning adenomas, and the rest are Rathke's cleft cysts,

lactotroph, somatotroph, and corticotropes adenomas in descending order of prevalence [70].

A lesion of 1 cm or more should have immediate check of vision (acuity and fields) as well as biochemical evaluation for hyperfunctioning and hypo functioning as well. Biochemistry includes insulin-like growth factor-1 (IGF-1), prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH) with testosterone or oestradiol, corticotropin (ACTH) with two out of three (24-hour urine free cortisol (UFC), dexamethasone suppression test or midnight salivary cortisol levels) and TSH with FT₄ [71,72]. In practice microadenoma (below 1 cm) hyperfunction of the lactotrophs, corticotropes, and somatotrophs should be looked for to rule out hyperprolactinemia, Cushing disease, and acromegaly respectively.

While in macroadenomas a full pituitary screen is checked. Apart from prolactinomas all functioning adenomas or nonfunctioning macroadenomas with visual or other neurological abnormalities should be evaluated for transsphenoidal surgery, lesions below 2 cm, nonfunctioning, and without visual abnormalities should be monitored by visual assessment, serial imaging, and hormonal assessment after six months, 12 month and annually thereafter [73]. No visual assessment or hormonal hyposecretion assessment is required for small lesions (smaller than 1 cm), only prolactin is checked if no signs of hormonal hypersecretion like acromegaly or Cushing as mentioned above which is more cost-effective approach than checking full pituitary screen panel and MRI 6 and 12 months [74].

Endocrine society advise for full pituitary panel and imaging in small lesions [75].

Follow up after initial screen is not recommended in lesion of 4 mm or below but annual MRI for two years is required for lesion between 5 to 9 mm, less frequently if lesion is stable [76]. In summary, check Prolactin, IGF-1, and cortisol excess if clinically indicated in an incidental microadenoma, MRI annually for two years if lesion is 0.5 to 0.9 mm, while in Macroadenoma the advice is to check the full pituitary hormonal pattern and MRI after six, twelve months and annual afterwards. Macroadenoma of more than 2 cm or causing mass effect should be referred to neurosurgeons urgently.

Functioning pituitary adenomas

Functioning gonadotrophs, and thyrotropes adenomas are rare and will not be mentioned here, however, adenomas of somatotrophs, corticotropes, and lactotrophs are common causing acromegaly in adults, Cushing disease, and prolactinoma respectively.

Hyperprolactinemia

Serum prolactin (SP) is secreted by the lactotroph cells of the pituitary gland, causes of hyperprolactinemia (levels more than 20 ng/mL) can be physiologic or pathologic. Physiologic causes are asymptomatic and lead to mild elevation and related to increase in oestrogen levels in pregnancy due to increase serum oestradiol, breastfeeding due to nipple stimulation, protein rich meals, and stress [77].

Pathologic causes of hyperprolactinemia include prolactinomas (lactotroph adenomas), microadenomas have size below 1 cm and usually increase prolactin level up to 200 ng/mL, macroprolactinomas of 1.0 to 2.0

cm can increase the prolactin level between 200 and 1000 ng/mL, while adenomas larger than 2.0 cm can increase levels above 1000 ng/mL, around 10 percent of prolactinomas can secrete growth hormone as well as prolactin [78].

However, nonfunctional macroadenomas can be associated with milder elevations of prolactin due to damage to the dopaminergic neurons of the hypothalamus and pituitary stalk by a large non-functioning adenoma. Hook effect which is an artifact in the immunoradiometric assay for prolactin, this artifact can underestimate the true level of prolactin and can be obviated by dilution of the serum [79].

Medication-induced hyperprolactinemia usually leads to a mild hyperprolactinemia with prolactin level up to 100 ng/mL, common medications are antipsychotics, metoclopramide, methyl dopa, H₂ blockers, and verapamil [80-82]. Familial hyperprolactinemia due to a mutation in the prolactin receptor gene (*PRLR*) is a rare cause of hyperprolactinemia, family history is usually positive [83]. Idiopathic hyperprolactinemia is a persistent mild elevation of prolactin levels without an obvious cause, however, following up these patients may show slight change in prolactin levels and rarely progression to prolactinoma [84]. Hypothyroidism can lead to enlargement of pituitary gland with hyperprolactinemia due to increase in TRH, prolactin values can return to normal after treating hypothyroidism [85]. Finally, hyperprolactinemia can occur due to reduced clearance as in cases of chronic kidney disease or macroprolactinemia, the last term is used to describe aggregates of prolactin with

antibodies, it is a benign condition which is irrelevant clinically and can be avoided by asking the laboratory to pretreat the serum with polyethylene glycol to precipitate the macroprolactin before the immunoassay for prolactin [86]. Hyperprolactinemia causes hypogonadism in premenopausal females by inhibiting gonadotropin-releasing hormone (GnRH) which in turn inhibits luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion leading to oligo/amenorrhea, infertility, galactorrhoea, and the reduction of oestradiol secretion leads to hot flashes and vaginal dryness [87]. Hyperprolactinemia leads to reduction in bone mineral density [88].

Postmenopausal women are in a state of hypogonadism by definition and identifying hyperprolactinemia can occur late (perhaps due to pressure effects of macroprolactinoma) or incidentally. Men with hyperprolactinemia can present with signs and symptoms of hypogonadotropic hypogonadism (low serum testosterone due to low LH) like infertility, decreased libido, and gynaecomastia with galactorrhoea, erectile dysfunction (ED) [89].

Treatment of hyperprolactinemia

Main two reasons for treating hyperprolactinemia are impending neurologic symptoms like headache or visual impairment due to a large lactotroph adenoma and hypogonadism [90].

Hyperprolactinemia in premenopausal women is associated with amenorrhea and low oestradiol levels (which lead to infertility, galactorrhoea, and osteoporosis). While men present with decreased libido, fatigue, infertility, and osteoporosis.

Hyperprolactinemia in men is associated with erectile dysfunction (ED), even if serum testosterone is normal [91]. Dopamine agonists decrease serum prolactin concentrations and reduces the size of most lactotroph adenomas [92].

Cabergoline is usually the first choice, it is administered once or twice a week with less side effects like nausea and more efficiency compared to Bromocriptine [93].

Concerns with chronic use of higher doses of Cabergoline (more than 2 mg per week) regarding valvular heart disease when regular echocardiography is indicated every two years, while this side effect is unusual in lower doses [94].

Other side effects of dopamine agonist include postural hypotension, mental fogging, and depression. Cabergoline has a higher risk of causing impulsive control disorders like gambling and hypersexuality [95]. Initial dose of Cabergoline is 0.25 mg twice a week or 0.5 mg once a week, while Bromocriptine which is preferable in pregnancy due to less risk of congenital anomalies, can be initiated at a dose of 1.25 mg once weekly. Both can be increased slowly until prolactin level normalise and adenomas shrinks [96].

Eighty percent of patients with hyperprolactinemia respond to cabergoline while 25% are resistant to Bromocriptine, switching to Cabergoline can be more effective in this case [97]. Transsphenoidal surgery is the last option in patients with macroadenoma who are resistant to oral treatment or sensitive to side effects, while clomiphene (ovulation induction) can be tried for women who are seeking pregnancy. Hormonal replacement is an option for men

or women who are not pursuing pregnancy (testosterone and oestrogen respectively). However, oestrogen treatment is contraindicated in macroprolactinoma. At least one year of treatment is required for patients with prolactinoma after achieving a normal prolactin level, withdrawing treatment gradually can be initiated after 2 years if no evidence of adenoma with normal prolactin level [93].

Quetiapine does not raise prolactin and aripiprazole has both dopamine agonist and antagonist properties, both are a good choice in hyperprolactinemia, of course after liaising with psychiatrist [98]. Idiopathic hyperprolactinemia causing hypogonadism is treated like prolactinoma, while macroprolactinoma doesn't require treatment as it is a lab error and asymptomatic and finally, hyperprolactinemia in the context of hypothyroidism is treated with levothyroxine.

Amenorrhoea

Primary amenorrhoea (PA) is absence of menarche by age of fifteen, while secondary menorrhea (SA) is absence of menses for more than three months in women who had regular menses or more than six months in women who had irregular menses [99].

The first thing to rule in/out in SA is pregnancy, other major causes of SA are disturbance in hypothalamus, pituitary, uterus, or ovaries. History taking may clarify the source of SA, functional hypothalamic is common and asking for symptoms like illness or stress, excessive exercise, change in eating habits or weight may point towards this diagnosis [100].

Medications like oral contraceptives may cause SA a few months after discontinuation,

medications which increases prolactin levels may also cause SA like citalopram, or androgens including progestin and danazol. Symptoms of hyperandrogenism like acne, hirsutism, and previous irregular menses can point towards polycystic ovary syndrome (PCO). Symptoms of mass effect from possible Sellar mass causing deficiency in pituitary and/or hypothalamus leading to visual impairment, headaches, diabetes insipidus, galactorrhea, or adrenal insufficiency [101].

Symptoms of oestrogen deficiency like painful intercourse due to vaginal dryness in sexually active women, hot flashes, night sweats, poor sleep, or decreased libido. Past medical history suggestive of gynecological cause of SA like previous procedures or pelvic inflammatory disease. Body mass index (BMI) can give a clue of the possible cause of SA, obesity is associated with PCO, while low BMI below 18 can be associated with functional hypothalamic disorder due to anorexia, illness, or strenuous exercise. Common investigations for SA are HCG (pregnancy), FSH, LH, oestradiol, Prolactin, and TSH. Low or normal oestradiol with raised FSH suggests ovarian failure, while low or normal FSH suggests central cause of SA (pituitary/hypothalamus disease) [102].

Serum total testosterone and 17-hydroxyprogesterone are measured if signs of hyperandrogenism (hirsutism, acne, previous irregular menses) to rule out/in PCO or atypical 21-hydroxylase deficiency. A fasting prolactin level can eliminate the usual rise due to physiological reasons like eating high protein diet, exercise, stress, and intercourse. Raised prolactin levels in absence of medications or hypothyroidism should be followed by an MRI of pituitary gland to rule

out prolactinoma. Paired TSH with free T₄ is indicated to rule out primary or secondary thyroid disease, treatment of primary hypothyroidism will reverse hyperprolactinemia due to raised hypothalamic thyrotropin-releasing hormone (TRH) [103]. Presence of high FSH with low Oestrogen suggests ovarian disease as mentioned above, while presence of low/normal FSH in the presence of low Oestradiol and normal prolactin and TSH suggests central cause of amenorrhea (pituitary or hypothalamus disease) or PCO. Serum FSH is higher than LH in functional hypothalamic disorder but lower than LH in PCO. Oestrogen is low in central causes but usually normal or high in PCO [104].

Other tests for a hypothalamic cause for SA are A₁C (diabetes mellitus), immunoglobulin A antibodies against tissue transglutaminase (coeliac disease), and transferrin sats with ferritin (haemochromatosis). DEXA scan for osteopenia/osteoporosis is indicated for patients with prolonged SA.

Galactorrhea

Physiological Galactorrhea occurs in pregnancy and chest wall irritation, but in absence of pregnancy a functioning pituitary adenoma or large nonfunctioning pituitary tumour should be ruled out as up to 20% of non-pregnant women with galactorrhea have a pituitary tumour, and in the presence of amenorrhea the likelihood of a pituitary tumour is one in three [105].

Prolactinoma is a common cause of galactorrhea as mentioned, women present with other signs of hyperprolactinemia like amenorrhea or reduced libido. Other malignancies that could potentially secrete prolactin are renal adenocarcinoma,

lymphoma, or bronchogenic carcinoma [106]. Other causes of hyperprolactinemia inducing galactorrhea should be looked for, like renal failure, acromegaly, Cushing syndrome, and primary hypothyroidism due to raised levels of TRH which increases TSH and prolactin levels.

Good history taking should clarify medications or herbal remedies ingestion. Many medications can increase prolactin levels, up to 15% of patients on antipsychotics can present with galactorrhea [107]. Tricyclic antidepressants, SSRI, and Bupropion can all lead to hyperprolactinemia [108].

Other common medications which can cause galactorrhea are H₂ blockers, atenolol, verapamil, and oral contraceptive pills [109-111]. Treatment of galactorrhea with hyperprolactinemia depends on the cause of hyperprolactinemia, in presence of hypothyroidism it is reasonable to start levothyroxine and assess prolactin levels with TSH after treatment, if galactorrhea is persistent after treating hypothyroidism and in absence of medications contributing to hyperprolactinemia, it is recommended to arrange for an MRI pituitary if prolactin levels are still high or local mass effect symptoms occur like headache or visual disturbance. If hyperprolactinemia inducing galactorrhea is persistent with or without evidence of prolactinoma treatment with Cabergoline is indicated to reduce the risk of osteoporosis and treat the galactorrhea, finally, if galactorrhea persists without evidence of hyperprolactinemia or medications (idiopathic), advise against breast stimulation or continuous expressing the discharge [112]. Idiopathic galactorrhea can occur with normal prolactin level and any cause of hyperprolactinemia may induce

galactorrhoea, risk for breast cancer is not increased with galactorrhoea [113].

Acromegaly clinical presentation

Hypersecretion of growth hormone (GH) directly stimulates insulin-like growth factor-1 (IGF-1) secretion from the liver, IGF-1 is responsible of the clinical features of acromegaly in adults. Common features of acromegaly occur slowly over a long period of time and involves the increase in size of hands, feet, jaw (prognathism) with spreading out of teeth, nose, and frontal bones. Obstructive sleep apnoea, hypertension, diabetes mellitus, carpal tunnel syndrome and pressure effect from large pituitary tumour causing visual loss and headache. IGF-1 secretion is not pulsatile with fluctuating levels like GH and the presence of raised levels of IGF-1 is pathognomonic for Acromegaly, however, if levels are equivocal with strong suspicion for Acromegaly, then oral glucose tolerance test (OGTT) can support the diagnosis of Acromegaly if GH fails to suppress [114]. Lower levels of IGF-1 occur in renal or liver failure, hypothyroidism, type one diabetes, and oestrogen, OGTT should be the next step if strong suspicion of acromegaly, also, GH is reduced in elderly and a normal level in the presence of clinical features could point towards Acromegaly [115].

OGTT is quite specific for Acromegaly, GH levels are checked before giving 75 g of glucose followed by a repeat GH level after two hours, failure to suppress GH level to 1 ng/mL or below points towards possible Acromegaly while levels more than 2 ng/mL is specific for Acromegaly [116]. The next step after confirming Acromegaly biochemically is imaging, pituitary MRI looking for

somatotroph adenoma (95% of cases of acromegaly) and up to 80% are macroadenomas, while ectopic GH releasing hormone (GHRH) secretion accounts for 0.5 % of cases and should be suspected if MRI fails to show an adenoma by checking the GHRH, finally if the levels are normal then the next step is searching for a extracranial GH secreting tumour [117].

Acromegaly treatment

Transsphenoidal surgery is the usual initial therapy for GH pituitary macroadenoma, debulk surgery followed by medical or radiotherapy is common for macroadenomas causing mass effect or acromegaly, However, treatment can present with complications diabetes insipidus, panhypopituitarism, cerebrospinal fluid rhinorrhoea, and meningitis [118]. Recommendations to repeat MRI, recheck IGF-1, and random growth hormone 12 weeks post operatively to decide whether adjuvant therapy is indicated or not, even a repeat surgery may be indicated if evidence of significant residual tumour which may be functional or nonfunctional and compressing the surrounding structures. Medical therapy with a somatostatin analogue with dopamine agonist in selected cases may be required if residual biochemical evidence of raised IGF-1 or failure to suppress Growth hormone in a patient is not a candidate for repeat surgery. Pegvisomant (blocks GH action) can be added if IGF-1 failed to reduce on a somatostatin analogue (Octreotide) or Dopamine agonist (Cabergoline) [114]. Radiation therapy can be used for non-operable patients whom medical treatment failed, or whom the size of the adenoma increased while on medical therapy. IGF-1 levels should be checked 3

monthly while on treatment, then less frequently if normalized. Therapeutic goals are a normal age-adjusted IGF-1 and a random GH below 1 mcg/L. MRI postoperatively as mentioned above should be checked after 3 months and then annually if normal. Colonoscopy should be performed as increased risk of colon polyps with Acromegaly [114]. Up to 70% of patients with Acromegaly develops GH deficiency after treatment (surgical or Radiotherapy), data is conflicting, GH deficiency can cause reduction in quality of life and replacing GH can reduce body fat, however, vascular events can occur after two years of GH therapy [119,120].

Somatostatin analogs inhibit GH secretion and can cause shrinkage to some adenomas [121]. Octreotide is given intramuscularly once a month with a starting dose of 20 mg to be increased up to 40 mg based on IGF-1 levels, while Lanreotide is given subcutaneously 60 then 120 mg and maximum dose 180 mg every month [122]. Pegvisomant is a GH receptor antagonist, administered as a daily subcutaneous injection, IGF-1 and not GH is used to monitor its efficacy as it inhibits GH action and not its secretion, monitor liver profile and stop the treatment if x_3 increase in upper range of normal [123]. Dopamine agonists, Cabergoline can be used as an add on or sole medication in cases of mild acromegaly with GH levels between 1-1.3 mcg/L. Initial dose 0.5 mg weekly or 0.25 mg twice weekly, dose can be increased slowly to a maximum of 2 mg weekly. Nausea is a common side effect; dizziness be effective and can cause valvular heart disease [124].

Radiotherapy is used as a second line after surgery or medical treatment as the reduction

of IGF-1 and GH can take few months to occur and up to 40% of patients may develop one or more pituitary hormone deficiency [125].

Hypercortisolism clinical features

The most common cause of hypercortisolism is iatrogenic Cushing syndrome from excess and prolonged steroid use, followed by Cushing disease (pituitary ACTH dependent), ectopic ACTH syndrome (paraneoplastic), then adrenal adenomas and tumours are least to cause Cushing syndrome [126].

Signs and symptoms of hypercortisolism depends on severity and duration of cortisol excess, clinical features like central obesity, hypertension, and diabetes can be mistaken for metabolic syndrome, while skin changes like purple striae with spontaneous bruises (due to connective tissue and skin atrophy), proximal muscle weakness, and facial plethora with increase in fat pad are more specific for cortisol excess [127]. Oligo/amenorrhoea common in women as hypercortisolism leads to reduction in gonadotropin-releasing hormone with subsequent reduction in LH and FSH/oestradiol, but hirsutism and acne (hyperandrogenism) only occur with ACTH dependent disease or adrenal cancer and not in hypercortisolism per say, while hyperpigmentation occurs only with ACTH dependent disease [128]. Cardiovascular disease is common in prolonged hypercortisolism due to accelerated atherosclerosis secondary to insulin resistance, diabetes, dyslipidaemia, and hypertension [129]. There is also an increased risk of thromboembolic disease due to glucocorticoid-induced increases in plasma concentrations of clotting factors [130]. Muscles weakness can be exacerbated by

hypokalaemia which occurs as excess cortisol has some aldosterone effect; this can lead to proximal skeletal muscle weakness and even respiratory failure in severe hypokalaemia [131]. Cortisol reduces intestinal calcium absorption with reduction in bone formation, and increase in bone resorption, all these effects lead to osteoporosis [132]. psychiatric manifestations like insomnia, anxiety, and depression are common than paranoid delusions in patients with hypercortisolism [133]. Glucocorticoids inhibit immune function by reducing cytokines levels, CD4 cells, and natural killer cell activity leading to increase in risk of infections with reduced inflammation despite the increase in neutrophil count [134].

Hypercortisolism investigations

Clinical features suggestive of Cushing syndrome are new diagnosis of severe or resistant hypertension in young patients, early osteoporosis, proximal muscle weakness with skin changes like purple striae with easily spontaneous bruising and facial plethora, new onset diabetes and central obesity with increase fat pad [135]. Prolonged use of steroid treatment can cause iatrogenic Cushing and is considered the most common cause now, drug history is essential, and investigations may not be required in the presence of prolonged steroid use with clinical features of hypercortisolism, however, if investigations are required, ACTH will be low in iatrogenic Cushing and even cortisol (serum and urine) can be low unless cortisone or cortisol is the medication used [136].

At least two out of three tests need to be abnormal to be considered a possible case of Cushing syndrome, first test is bedtime

salivary cortisol, second test is 24-hour urinary free cortisol (UFC), and finally, 1 mg overnight dexamethasone suppression test (DST) when 1 mg of Dexamethasone is given just before midnight and cortisol levels are checked 8 am the following morning, normal cortisol response is level below 50 nmol/L, DST is not reliable if patient is pregnant, on oestrogen therapy or diabetic, salivary and UFC are recommended to be repeated twice to increase sensitivity [135]. False positive bedtime salivary cortisol can occur in patients who work night shifts, also, false positive DST can occur in women who take oral oestrogen which increases the corticosteroid-binding globulin. Further cause of false positive tests is pseudo-Cushing, which is a physiological cortisol excess due to pregnancy, polycystic ovary syndrome, anxiety, depression, anorexia nervosa, or chronic alcoholism, interestingly patients with physiological cortisol excess do tend to lack the purplish striae, proximal myopathy, or spontaneous easy bruising and 24 UFC excretion is abnormal but usually below x3 the upper reference value [137].

When Cushing syndrome is confirmed and iatrogenic or physiological hypercortisolism is ruled out, the following step is to search for the source of Cushing syndrome. ACTH dependent Cushing syndrome is excessive corticotropin (ACTH) secretion whether from the pituitary gland or nonpituitary secreting tumour, while ACTH independent occurs by autonomous adrenal secretion of cortisol which is unrelated to ACTH.

Therefore, the initial step is to check morning ACTH level at least twice as secretion of ACTH is pulsatile or episodic, if ACTH level is low (below 5 pg/ml) this points towards ACTH independent disease, while if ACTH is

above 20 pg/ml this is suggestive of ACTH dependent disease (pituitary or ectopic) [138].

Often ACTH levels are between 5-20, in this scenario the advice is to recheck UFC or salivary cortisol weekly and assuming still showing hypercortisolism repeat ACTH after 4-6 weeks or checking dehydroepiandrosterone sulphate (DHEAS) which is raised or normal in ACTH dependent disease but reduced in adrenal causes of hypercortisolism [139].

ACTH-dependent Cushing syndrome (over 20 pg/mL) commonly originates from a pituitary adenoma (Cushing disease) compared to ectopic ACTH secretion. High dose dexamethasone test (8 mg dexamethasone instead of 1 mg) can suppress ACTH and cortisol in Cushing disease but not ectopic ACTH, which is resistant to steroids, however, fifty percent of patients with Cushing disease may not respond [140].

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Ectopic ACTH-secreting tumours (mostly in chest) are usually diagnosed with (CT or positron emission tomography) [143]. ACTH-

independent disease (below 5 pg/mL) points towards adrenal source of hypercortisolism like adenoma, carcinoma, or hyperplasia. CT is superior to MRI initially as it provides Hounsfield unit information. Hounsfield unit <10 points towards a benign functioning adenoma while the presence of calcification, haemorrhage, or necrosis points towards carcinoma which is usually larger than 4 cm in size, also, if adrenal androgens are elevated (with low ACTH) this may point towards carcinoma [144].

Treatment of ACTH dependent disease due to pituitary adenoma (Cushing disease) is transsphenoidal microadenomectomy (partial hypophysectomy) however, it is important to bear in mind that the more extensive the resection, the greater the risk of panhypopituitarism [145]. Medical therapy is often required if surgery is contraindicated or unsuccessful, drugs that target corticotroph adenoma like Pasireotide and Cabergoline can normalize UFC in up to 40% of cases, while Mifepristone (glucocorticoid and progestin antagonist) is approved for the treatment of glucose intolerance in Cushing syndrome) [146].

Pituitary irradiation by megavoltage linear accelerator can correct hypercortisolism after surgery within 12 months and in up to 85% of cases and similar success rate if used as a monotherapy in children [145]. Bilateral adrenalectomy with glucocorticoid and mineralocorticoid replacement therapy is the final solution when surgery, radiotherapy or medication fail [147]. Ectopic ACTH tumours are common in chest, surgical excision of pulmonary carcinoid without metastasis achieved normal cortisol levels in majority of patients [148].

Final few words on diabetes insipidus (DI)

Vasopressin or antidiuretic hormone (ADH) is synthesised by the hypothalamus then stored in vesicles and transported down the hypothalamic-hypophyseal tract via axons and finally released by the posterior pituitary [149].

ADH function is to maintain the homeostasis of osmolality or tonicity, slight increase in plasma osmolality results in increased secretion of ADH which in turn acts on the V receptor in collecting ducts at kidneys leading to increase in water reabsorption returning the plasma osmolality to normal range [150].

ADH secretion is also stimulated by the baroreceptors when there is a decline in blood volume and pressure, in higher concentrations ADH causes vasoconstriction by stimulating V receptors on vascular smooth muscles with water retention these two mechanisms lead to elevation of blood pressure by increasing the load and the resistance [150].

Other factors which increase ADH secretion apart from raised osmolality and reduced blood volumes are the factors which lead to syndrome of inappropriate ADH (SIADH), like pain, nausea, nicotine, opiates, pulmonary and intracranial diseases, and certain medications like SSRI, worth mentioning that alcohol reduces ADH and leads to excess diuresis in intoxicated patients [151]. Central diabetes insipidus (DI) is a condition of ADH deficiency that occurs due to damage of the hypothalamus or posterior pituitary glands resulting in excess free water excretion by kidneys. Clinically the patient with DI is complaining of polyuria (more than

3 L per day or more than 40 mls/Kg/day) and polydipsia with low urinary osmolality and hypernatremia with raised plasma osmolality. Nephrogenic DI is a condition of ADH resistance, kidneys are resistant to the effect of ADH rather than deficiency. Common causes are lithium or tetracycline, hypercalcaemia or hypokalaemia, and inherited mutations in V receptors [152].

SIADH is a common cause of hyponatraemia in euvoletic patients. Euvolemia occurs as water retention causes an increase in sodium excretion by urine and often water follows, and this is the main reason of absence of signs of fluid overload like oedema. Diagnostic criteria are euvoletic hyponatremia, low plasma osmolality (<275 mOsm/kg), urine osmolality >100 mOsm/kg, elevated urine sodium (>20 mEq/L) in presence of normal renal, thyroid, and adrenal functions. Differential diagnosis of DI is diabetes mellitus and primary polydipsia, water deprivation challenge in absence of diabetes mellitus can differentiate DI from primary polydipsia. During water deprivation urine osmolality increases to above 750 mOsm/kg which points towards primary polydipsia as with DI urine osmolality remains low (below 300 mOsm/Kg).

To differentiate between nephrogenic and central DI, desmopressin is given and if urine osmolality increases, then central DI is present [152].

Conclusion

Pituitary gland disorders are common and can be life threatening, awareness of the clinical features of pituitary hormones hypersecretion and deficiency is important, basic biochemical investigations include full

pituitary hormonal panel in early morning paired with target glands hormones to be able to assess primary from secondary causes. Full pituitary hormones are needed when suspicion of panhypopituitarism is high and if a large tumour is expected to cause deficiency due to pressure on pituitary tissue. While in a microadenoma the important tests required are IGF-1, ACTH, and prolactin as microadenoma should not cause pressure effect but hormone excess. Finally, local mass

effect causing headache and visual disturbance should be checked by an MRI pituitary gland with contrast and formal visual field examination, and pituitary apoplexy which is an emergency requires high suspicion when patients with or without known pituitary tumour present with thunderclap headache, visual disturbance and low conscious level as steroid deficiency which is acute in this case can be life-threatening.

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