Endocrinal Dysfunction in Pituitary Tumors

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Anatomy and Physiology

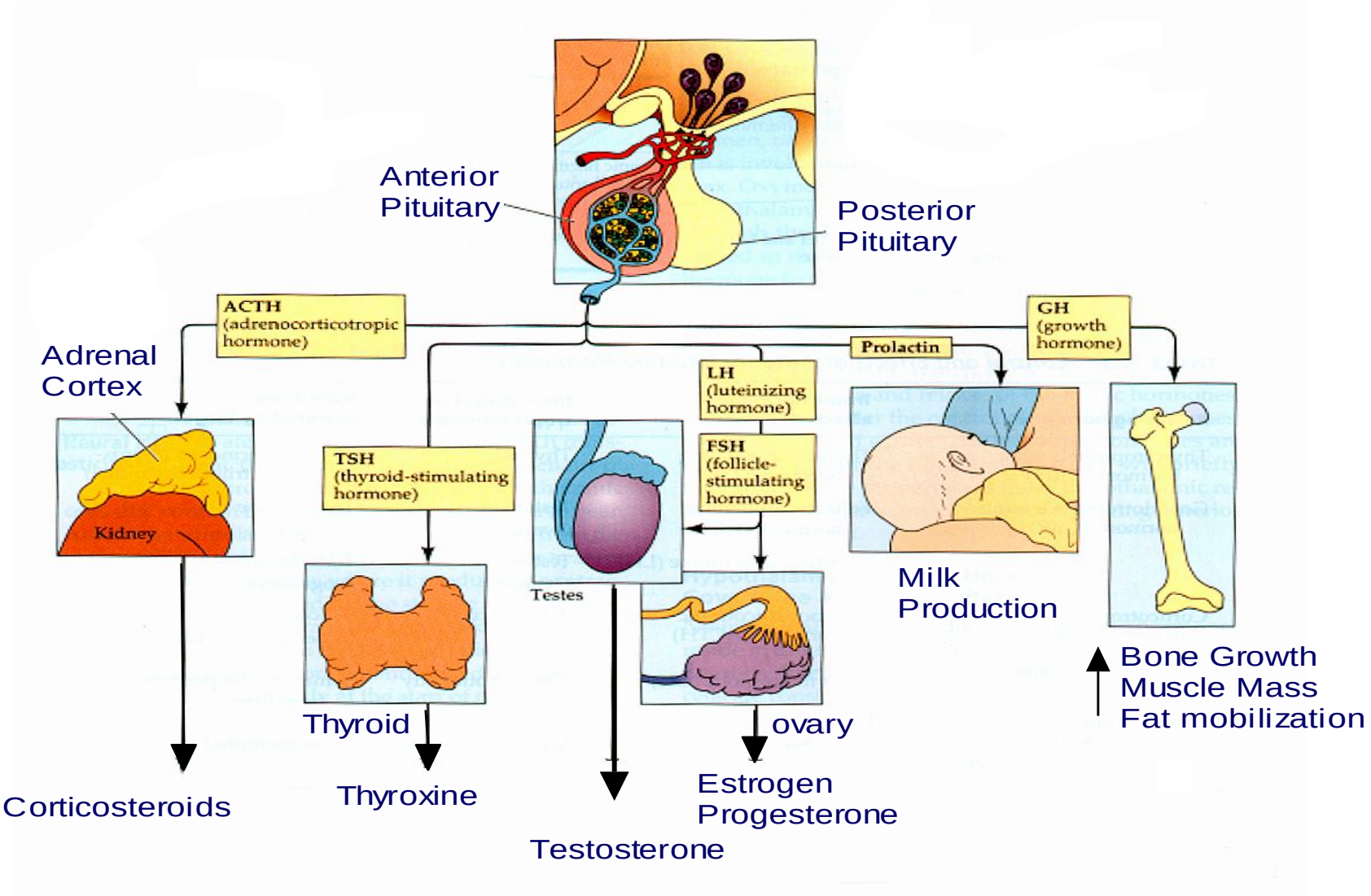
- The pituitary is referred to as the "master gland."
- It weighs only about 0.5 g.
- It is divided into:
  - adenohypophysis
  - neurohypophysis
- The pituitary stalk transmits:
  - regulatory hormones.
  - the axons of the hypothalamus.
- The optic chiasm is 5 to 10 mm above the diaphragma sella [(1)].
- Secretes eight hormones that are critical to survival [(1)].

Hormones of the Anterior Pituitary

Five cell types produce six major hormones.
These are:

1. Mammotrophs produce Prolactin (acidophilic)
2. Somatotrophs produce Growth H (acidophilic)
3. Corticotrophs produce ACTH, MSH, and various endorphins (basophilic)
4. Thyrotrophs produce TSH (basophilic)
5. Gonadotrophs produce FSH and LH (basophilic)

Hormones of the Anterior Pituitary



Pituitary releasing/inhibing hormones

1. CRH: Corticotrophin releasing hormone
2. TRH: Thyrotrophin releasing hormone
3. GHRH: GH releasing hormone
4. Somatostatin: GH inhibition
5. GnRH: Gonadotrophin (LH, FSH) releasing hormone
6. Dopamine: Prolactin inhibition

Hormones of the Anterior Pituitary (1)

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

Pituitary hypersecretion syndromes (1)

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

1- Prolactin

PRL

Abnormality of Prolactin

- ***Prolactinoma***

It is the most frequent hyperfunctioning pituitary adenoma.

20% to 30% of pituitary tumors

50% of all functioning pituitary tumors.

Not associated with significant mortality.

In women, amenorrhea, galactorrhea, loss of libido, and infertility.

In men, decreased libido, impotence, premature ejaculation, erectile dysfunction, and oligospermia [(2)].

Abnormality of Prolactin

Diagnosis of Prolactinoma

Prolactin is markedly increased (eg, >500 mg/L) with a visible pituitary adenoma on MRI.

Prolactin levels parallel tumor size; most prolactinomas greater than 1 cm have prolactin concentrations greater than 250 mg/L [(3)].

Hyperprolactinemia in the absence of a pituitary tumor should prompt assessment for other causes.

Abnormality of Prolactin

Treatment of prolactinoma

Medical therapy

Dopamine agonists:

- The ergot derivatives, as
  - bromocriptine, pergolide and cabergoline.
- The non-ergot derivatives, like
  - quinagolide.

Abnormality of Prolactin

Surgical treatment

The trans-sphenoidal approach is the standard of care [4].

Radiotherapy

Indicated in resistance to dopamine agonists and surgery, with a proven trend to growth [5].

Abnormality of Prolactin

- ***Prolactin deficiency***

It is a marker of severe pituitary damage [6].

In women, it can cause failure of lactation.

In men, a phenotype has yet to be established [7].

2- Growth Hormone

GH

Abnormalities of Growth Hormone

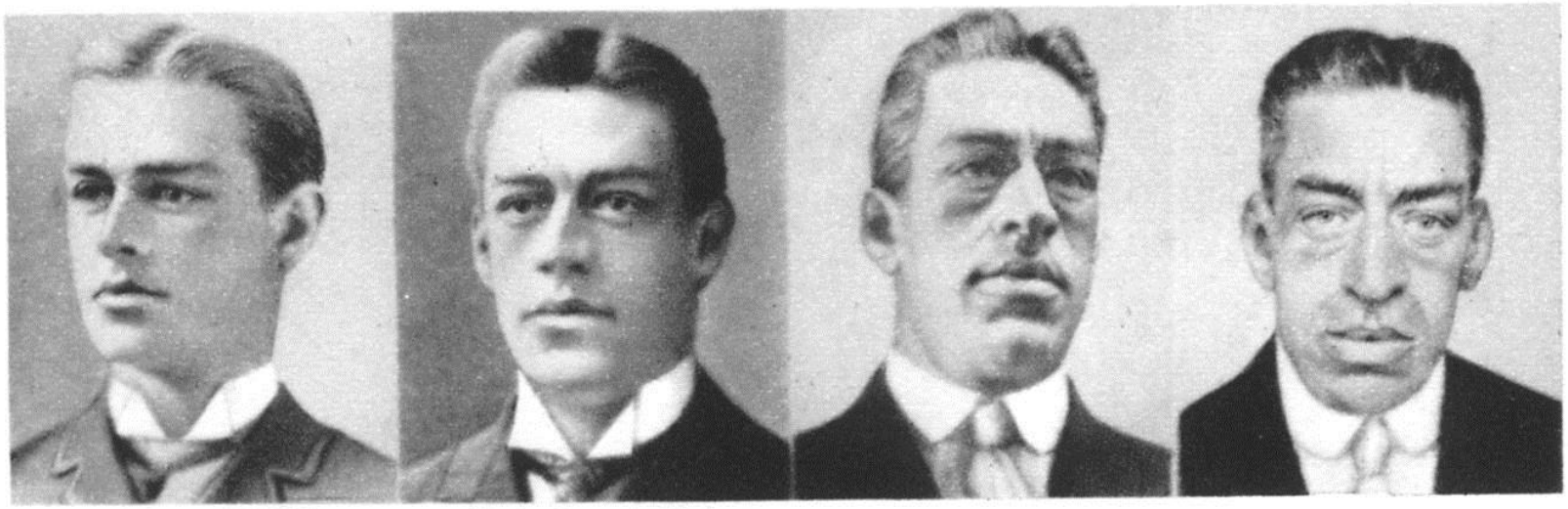
- ***Hypersecretion (Gigantism and Acromegaly)***

It leads to overproduction of IGF-1 by the liver.

Children experience gigantism while acromegaly develops in adults.

Patients have a characteristic features.

Abnormalities of Growth Hormone



Age 9

Age 16

Age 33

Age 52

Abnormalities of Growth Hormone

Laboratory Diagnosis

Random GH is unreliable (due to pulsatile nature of GH secretion) [8].

Measurement of IGF-1 is the recommended screening test [9].

Dynamic testing with oral glucose tolerance test should be done [10].

Abnormalities of Growth Hormone

Treatment of Acromegaly

Surgery for acromegaly·

Transsphenoidal adenomectomy.

The most sensitive predictor of outcome is a GH concentration within the first week after operation that is less than 2 µg/l [11].

Medical treatment of acromegaly [2].

1. Somatostatin receptor ligands (SRLs).
   - First-generation: (eg octreotide and lanreotide).
   - Second-generation: (eg pasireotide).
2. Dopamine agonists.
3. The GH-receptor antagonist pegvisomant (Somavert).

Abnormalities of Growth Hormone

Commercially available medical therapy for acromegaly [12]:

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.

Abnormalities of Growth Hormone

- ***Growth hormone deficiency***

Children present with short stature for their age [13].

Adults are insulin resistant and the serum lipid profile is abnormal [14].

Patients have reduced bone mineral density with increased fracture [15].

Treatment

0.2 mg somatotrophin SC once a day initially.

The dose is increased if necessary aiming at an age adjusted IGF-I [16].

3- Adrenocorticotropic Hormone

ACTH

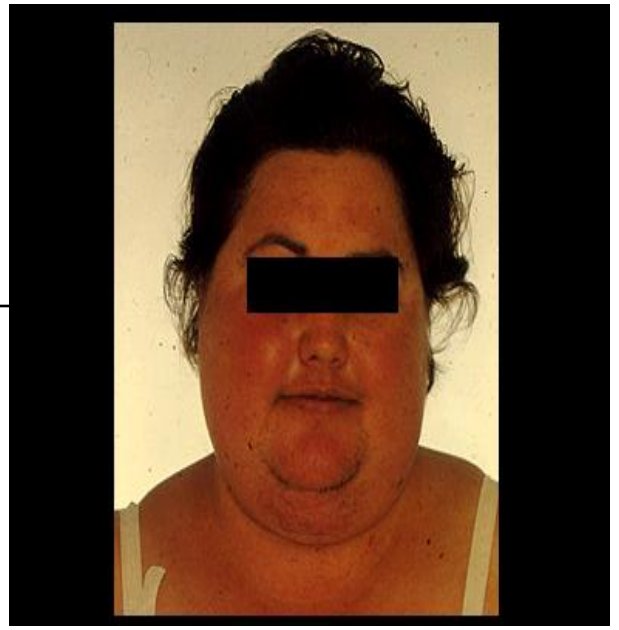
Abnormalities of ACTH

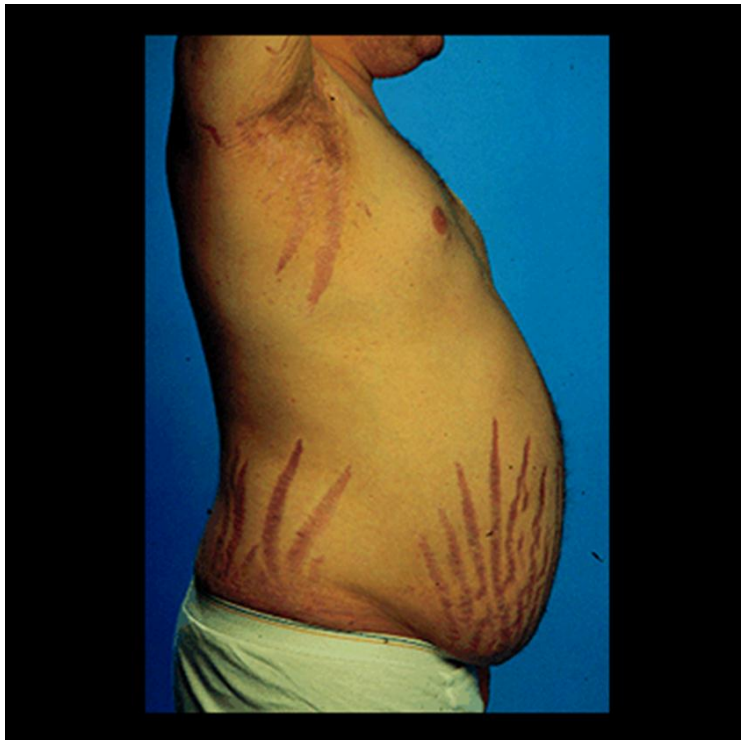
- ***Cushing Disease***

Hypersecretion of ACTH by a pituitary adenoma with hypercortisolism.

Centripetal obesity, pigmented striae, mood lability, proximal muscle weakness, HTN, DM2, hypogonadism

Patients are typically obese with characteristic "moon facies."





Abnormalities of ACTH

Laboratory Diagnosis

This can be assessed using 3 biochemical tests:

(1) 24-hour urinary free cortisol excretion.

(2) late night salivary cortisol collection.

(3) 1 mg dexamethasone suppression test.

At least 2 tests must be abnormal to establish the diagnosis of Cushing's syndrome [17].

High-dose dexamethasone suppression tests or sampling of ACTH levels in the inferior petrosal sinus are used to localize ACTH overproduction to the pituitary [18].

Abnormalities of ACTH

Treatment of Cushing's syndrome

- *Surgical Treatment*

Transsphenoidal selective tumor resection (TSS) [19].

- Medical therapy

Treatments include steroidogenesis inhibitors, tumor-directed drugs, and glucocorticoid receptor antagonists [20].

A combination of drugs may be necessary to achieve eucortisolism.

- Radiotherapy

A second-line for persistent or recurrent disease after TSS [19].

Abnormalities of ACTH

Summary of drugs for Cushing's syndrome [21].

Drug	Dose	Main side-effects
Pituitary tumour-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, edema, and hypokalaemia

Abnormalities of ACTH

- Bilateral adrenalectomy [22]

It is a treatment option for Cushing's syndrome.

Patients need life-long glucocorticoid and mineralocorticoid replacement.

Nelson's syndrome

It is defined by the association of a pituitary macroadenoma and high ACTH secretion after adrenalectomy leading to hyperpigmentation.

Such tumors can be very invasive, extending into surrounding structures.

Today, NS is revisited using more sensitive diagnostic tools to evaluate corticotroph tumor progression after adrenalectomy [23].

Abnormalities of ACTH

- ***Adrenocorticotropin deficiency***

It is the most serious of anterior pituitary hormone deficits [7].

Adrenal crisis with severe hyponatremia and hypovolemic shock may develop and can result in death.

Treatment is by hormonal replacement

4- Thyorid Stimulationg Hormone

TSH

Abnormalities of Thyrotropin

- ***TSH-secreting pituitary adenoma:***

Patients are frequently misdiagnosed as Graves' disease, and had thyroid ablation [24].

Hyperthyroidism may be overshadowed by concomitant acromegaly, or by neurological compression symptoms [25].

Disorders of the gonadal axis are frequent.

Serum TSH and circulating free thyroid hormones are raised.

Abnormalities of Thyrotropin

Treatment

Trans-sphenoidal or subfrontal approach.

Some adenomas are 'pituitary stones' and may be locally invasive [26].

Anti-thyroid drugs to restore euthyroidism before surgery.

The medical treatment rests on long-acting somatostatin analogues [27].

If surgery is contraindicated, pituitary radiotherapy should be considered [25].

Abnormalities of Thyrotropin

- ***Thyrotropin deficiency***

Clinically similar to primary hypothyroidism but usually less severe.

Thyrotropin deficiency usually occurs late in hypopituitarism and often is seen with other anterior pituitary hormone deficits.

T4 replacement therapy may be necessary [25].

5- Gonadotrophic Hormones

FSH and LH

Abnormalities of Gonadotropin

- ***Gonadotroph pituitary adenomas***

The majority of the previously labeled non-functional tumors were indeed secreting FSH, LH, or both.

The clinical behavior is like inactive tumors [28].

They account for 10–15% of all pituitary adenomas.

True "null-cell adenomas" represent 5– 10% of all pituitary tumors.

They are large and often have extension beyond the sella tursica.

The mechanical effects of the macroadenoma include hypopituitarism [29].

Hormone-related symptoms are rare.

Abnormalities of Gonadotropin

Treatment of gonadotroph adenomas

Surgery

Transsphenoidal surgical adenomectomy.

Medical therapy

There is no effective medical treatment, and thus the management does not differ from null-cell adenomas.

Radiation therapy

Radiation therapy can be used for residual or recurrent tumors [30].

Abnormalities of Gonadotropin

- ***Gonadotropin deficiency***

Differs clinically according to the gender and age of onset.

In men, the symptoms may not become evident, particularly if fertility is not an issue.

- Slow beard growth, loss of body hair, thin skin.
- Decreased libido, weak erection, azoospermia

Conversely, in women, it is diagnosed quickly when oligomenorrhea or amenorhea develops..

6- Antidiuretic Hormone

ADH

Posterior pituitary: ADH

Diabetes Insipidus and Syndrome of Inappropriate Antidiuretic Hormone [31].		
	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)

Hypopituitarism

Hypopituitarism is a rare condition [32].

It describes the deficiency of one or more of the anterior or posterior pituitary hormones .

Panhypopituitarism often describes anterior pituitary hormone deficiency while posterior pituitary function may be intact [7].

The recent recognition of causes, such as head injury and cranial radiotherapy, will result in an increase in prevalence.

Hypopituitarism

Clinical features of hypopituitarism

Deficits may be secondary to functional pituitary tumors, for example, suppression of gonadotropins in hyperprolactinemia or GH deficiency caused by cortisol excess in Cushing's syndrome [33].

The deficits may recover when the underlying endocrinopathy is treated.

Symptoms attributed to the local effects of the tumor include headaches, visual disturbance, or cerebrospinal fluid rhinorrhea [7].

Pituitary apoplexy

Hemorrhagic infarction of the pituitary tumor with sudden onset of severe headache, n/v, vision loss and cranial nerve palsies.

Clinically significant pituitary apoplexy is a rare event in patients with pituitary microadenomas [34].

If untreated, hypotension and shock secondary to adrenal insufficiency as well as irreversible vision loss or diplopia can occur [35].

Surgical intervention is recommended within 24–48 h of onset.

Conclusion

- Prolactinomas and nonfunctioning adenomas are the most common types of pituitary tumors.
- They may present initially with symptoms of endocrine dysfunction, or with mass effects.
- The diagnosis may also be made incidentally; the so called pituitary incidentaloma.
- Oversecretion of hormones may result in classic clinical syndromes such as hyperprolactinemia, acromegaly, and Cushing disease.
- In the diagnostic approach, it is important to evaluate complete pituitary function, because hypopituitarism is common.
- Therapy depends on the specific type, and should be managed with a team approach to include endocrinology and neurosurgery.

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