University of Baghdad
College of Medicine
2023-2024

Title: The pituitary gland/ first lecture

Grade: 4th year

Module: Endocrinology

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Date: at Monday 25/3/2024

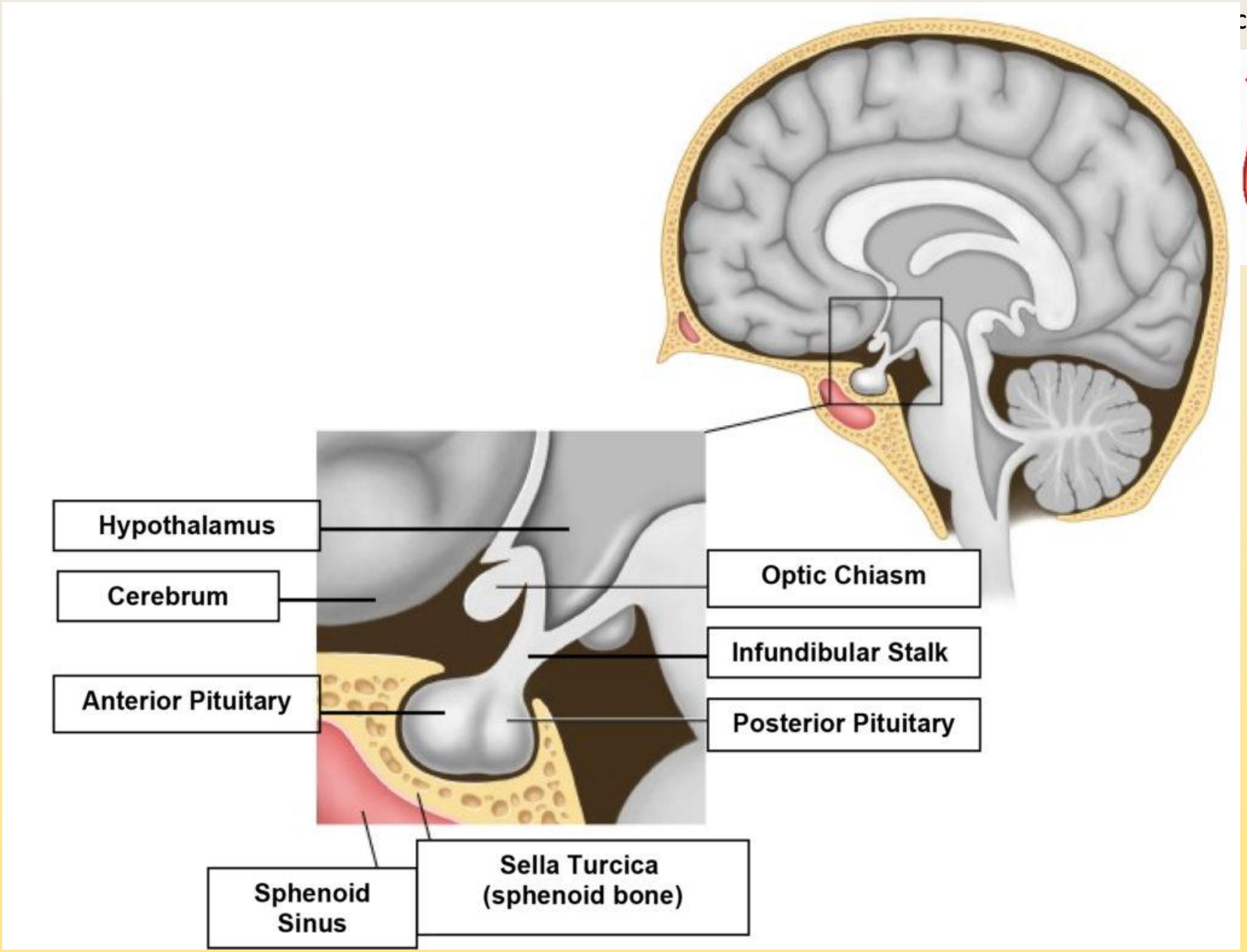
objectives

- Discus briefly the pituitary gland anatomy & physiology.
- Explain the hormonal & radiological investigations used in pituitary hormone excess & deficiency.
- Discus the histology of the pituitary adenomas.
- Explain in details the Presenting problems in pituitary diseases.
- Discus extensively hypopituitarism.
- Discus extensively pituitary tumors.

The pituitary gland

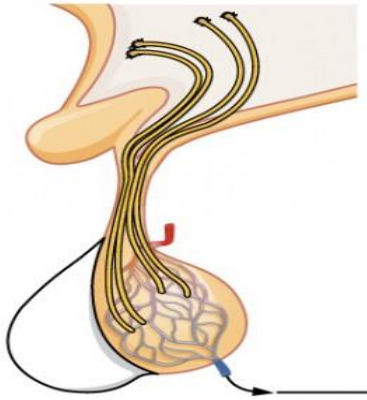
- The pituitary measures around 13mm transversely, 9mm anteroposteriorly, and 6mm vertically and weighs ~100mg.
- The pituitary gland is centrally located at the base of the brain in the sella turcica within the sphenoid bone. It is enclosed in the sella turcica and bridged over by a fold of dura mater called the diaphragma sellae, with the sphenoidal air sinuses below and the optic chiasm above. The cavernous sinuses are lateral to the pituitary fossa and contain the 3rd, 4th and 6th cranial nerves and the internal carotid arteries.

- The gland is composed of two lobes, anterior and posterior, and is connected to the hypothalamus by the infundibular stalk, which has portal vessels carrying blood from the median eminence of the hypothalamus to the anterior lobe and nerve fibers to the posterior lobe.
- The gland is composed of glandular tissue in the anterior pituitary (adenohypophysis) and neural tissue in the posterior pituitary (neurohypophysis).


Hypothalamus
Cerebrum
Anterior Pituitary
Optic Chiasm
Infundibular Stalk
Posterior Pituitary
Sphenoid Sinus
Sella Turcica (sphenoid bone)

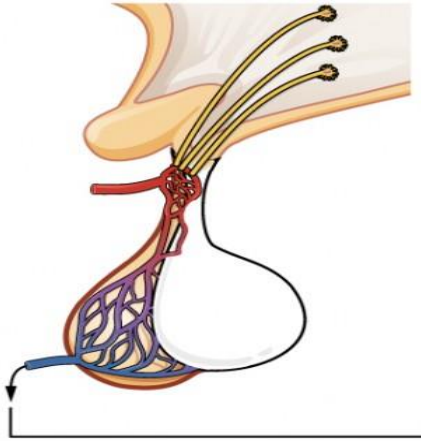
physiology

Posterior Pituitary Hormones



Releasing hormone (hypothalamus)	Pituitary hormone	Target	Effects
ADH	Stores ADH	Kidneys, sweat glands, circulatory system	Water balance
–	OT	Female reproductive system	Triggers uterine contractions during childbirth

Anterior Pituitary Hormones



Releasing hormone (hypothalamus)	Pituitary hormone	Target	Effects
GnRH	LH	Reproductive system	Stimulates production of sex hormones by gonads
GnRH	FSH	Reproductive system	Stimulates production of sperm and eggs
TRH	TSH	Thyroid gland	Stimulates the release of thyroid hormone (TH). TH regulates metabolism.
PRH (inhibited by PIH)	PRL	Mammary glands	Promotes milk production
GHRH (inhibited by GHIH)	GH	Liver, bone, muscles	Induces targets to produce insulin-like growth factors (IGF). IGFs stimulate body growth and a higher metabolic rate.
CRH	ACTH	Adrenal glands	Induces targets to produce glucocorticoids, which regulate metabolism and the stress response

Investigations of patients with pituitary disease

TABLE 17. Initial Testing for Pituitary Hormone Deficiency and Excess

Pituitary Hormone Excess

Pituitary Hormone	Peripheral Hormone	Initial Test(s)
ACTH	Cortisol	24-H urine free cortisol (×2) OR nocturnal salivary cortisol (×2) OR overnight low-dose dexamethasone test
ADH	ADH	Simultaneous serum sodium, serum osmolality, urine sodium, and urine osmolality
GH	IGF-1	IGF-1
TSH	Thyroxine, triiodothyronine	TSH, free (or total) thyroxine
PRL	Prolactin	Prolactin

Pituitary Hormone Deficiency

Pituitary Hormone	Peripheral Hormone	Initial Test(s)	Confirmatory Test[a]
ACTH	Cortisol	Simultaneous 8 AM ACTH, cortisol	ACTH stimulation test
ADH	ADH	Simultaneous serum sodium, urine and serum osmolality	Water deprivation test
LH and FSH[b]	Testosterone or estradiol	Simultaneous LH, FSH, 8 AM total testosterone (male), estradiol (female)	
TSH	Thyroxine, triiodothyronine	Simultaneous TSH, free (or total) thyroxine	
GH	IGF-1	IGF-1	GHRH-arginine Insulin tolerance Glucagon stimulation Ghrelin agonist stimulation

ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; GHRH = growth hormone–releasing hormone; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; PRL = prolactin; TSH = thyroid-stimulating hormone.

[a]See Table 19 for additional information on confirmatory testing for pituitary dysfunction.

[b]Routine testing for deficiency is not recommended without specific signs of deficiency, such as amenorrhea, gynecomastia, or impotence.

Radiological investigations: Establish the anatomy and diagnosis

- MRI reveals ‘abnormalities’ of the pituitary gland in as many as 10% of ‘healthy’ middle-aged people. It should therefore be performed only if there is a clear biochemical abnormality or if a patient presents with clinical features of pituitary tumor. A pituitary tumour may be classified as either a macroadenoma (> 10 mm diameter) or a microadenoma (< 10 mm diameter).

- The most common local complication of a large pituitary tumour is compression of the optic pathway. The resulting visual field defect can be documented using a Goldman's perimetry chart.

Establish the anatomy and diagnosis

- Consider visual field testing
- Image the pituitary and hypothalamus by MRI or CT

Histology

- Conventional histology identifies tumors as:
  - chromophobe (usually non-functioning).
  - acidophil (typically prolactin- or growth hormone-secreting).
  - basophil (typically ACTH-secreting).
- Immunohistochemistry may confirm their secretory capacity but is poorly predictive of growth potential of the tumour.

Presenting problems in pituitary diseases

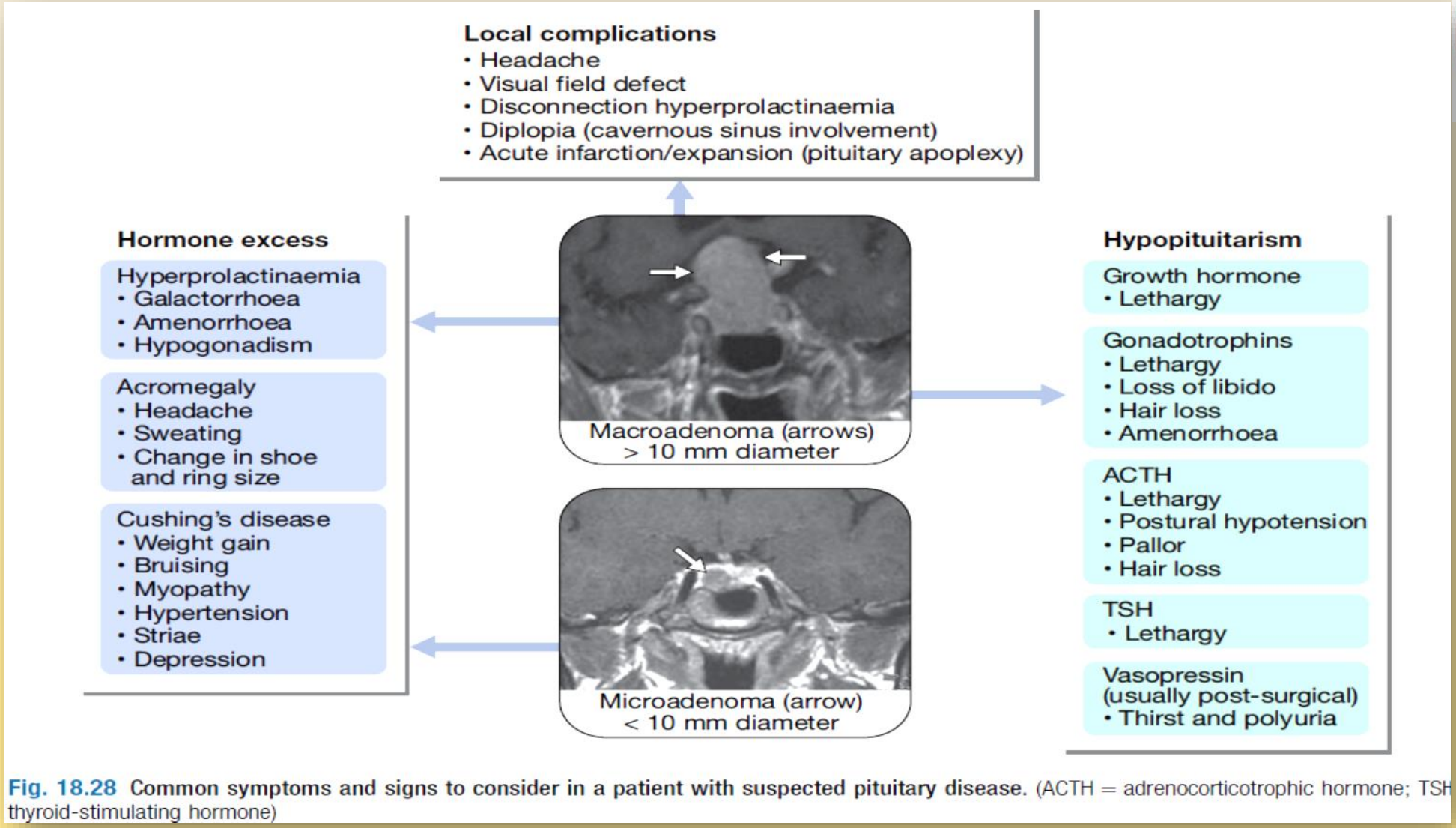


Fig. 18.28 Common symptoms and signs to consider in a patient with suspected pituitary disease. (ACTH = adrenocorticotrophic hormone; TSH thyroid-stimulating hormone)

18.52 Classification of diseases of the pituitary and hypothalamus

	Primary	Secondary
Non-functioning tumours	Pituitary adenoma Craniopharyngioma Metastatic tumours	
Hormone excess		
Anterior pituitary	Prolactinoma Acromegaly Cushing's disease Rare TSH-, LH- and FSH-secreting adenomas	Disconnection hyperprolactinaemia
Hypothalamus and posterior pituitary	Syndrome of inappropriate antidiuretic hormone (SIADH, p. 357)	
Hormone deficiency		
Anterior pituitary	Hypopituitarism	GnRH deficiency
Hypothalamus and posterior pituitary	Cranial diabetes insipidus	(Kallmann's syndrome)
Hormone resistance	Growth hormone resistance (Laron dwarfism) Nephrogenic diabetes insipidus	

(FSH = follicle-stimulating hormone; GnRH = gonadotrophin-releasing hormone; LH = luteinising hormone; TSH = thyroid-stimulating hormone)

Hypopituitarism

- Hypopituitarism refers to either partial or complete deficiency of anterior and/or posterior pituitary hormones and may be due to 1° pituitary disease or to hypothalamic pathology which interferes with the hypothalamic control of the pituitary.
- The clinical presentation is variable and depends on the underlying lesion and the pattern of resulting hormone deficiency. The most common cause is a pituitary macroadenoma.

18.54 Causes of anterior pituitary hormone deficiency

Structural

- Primary pituitary tumour
- Adenoma*
- Carcinoma (exceptionally rare)
- Craniopharyngioma*
- Meningioma*
- Secondary tumour (including leukaemia and lymphoma)
- Chordoma
- Germinoma (pinealoma)
- Arachnoid cyst
- Rathke's cleft cyst
- Haemorrhage (apoplexy)

Inflammatory/infiltrative

- Sarcoidosis
- Infections, e.g. pituitary abscess, tuberculosis, syphilis, encephalitis
- Lymphocytic hypophysitis
- Haemochromatosis
- Langerhans cell histiocytosis

Congenital deficiencies

- GnRH (Kallmann's syndrome)*
- GHRH*
- TRH
- CRH

Functional*

- Chronic systemic illness
- Anorexia nervosa
- Excessive exercise

Other

- Head injury*
- (Para)sellar surgery*
- (Para)sellar radiotherapy*
- Post-partum necrosis (Sheehan's syndrome)
- Opiate analgesia

*The most common causes of pituitary hormone deficiency.
(CRH = corticotrophin-releasing hormone; GHRH = growth hormone-releasing hormone; GnRH = gonadotrophin-releasing hormone; TRH = thyrotrophin-releasing hormone)

The clinical features

- The clinical features depend on the type and degree of the hormonal deficits and the rate of its development, in addition to whether there is intercurrent illness.
- In the majority of cases, the development of hypopituitarism follows a characteristic order, with secretion of GH, then gonadotrophins being affected first, followed by TSH and ACTH secretion at a later stage. PRL deficiency is rare, except in Sheehan's syndrome associated with failure of lactation.
- Antidiuretic hormone (ADH) deficiency is virtually unheard of with pituitary adenomas but may be seen rarely with infiltrative disorders and trauma.

- **Growth hormone** deficiency in adults produces lethargy, muscle weakness and increased fat mass but these features are not obvious in isolation.
- **gonadotrophin (LH and FSH)** deficiency causes loss of libido in the male and oligomenorrhoea or amenorrhoea in the female. Later, in the male there may be gynecomastia and decreased frequency of shaving. In both sexes, axillary and pubic hair eventually become sparse or even absent and the skin becomes characteristically finer and wrinkled. Chronic anemia may also occur.

- **ACTH** deficiency resulting in symptoms of cortisol insufficiency (including postural hypotension and a dilutional hyponatraemia), but with a striking degree of pallor is usually present & normal plasma potassium(in contrast to primary adrenal insufficiency).

- TSH deficiency causes secondary hypothyroidism, this contributes further to apathy and cold intolerance. In contrast to primary hypothyroidism, frank myxoedema is rare, presumably because the thyroid retains some autonomous function.

- The onset of all of the above symptoms is notoriously insidious. However, patients sometimes present acutely unwell with glucocorticoid deficiency. This may be precipitated by a mild infection or injury, or may occur secondary to pituitary apoplexy.

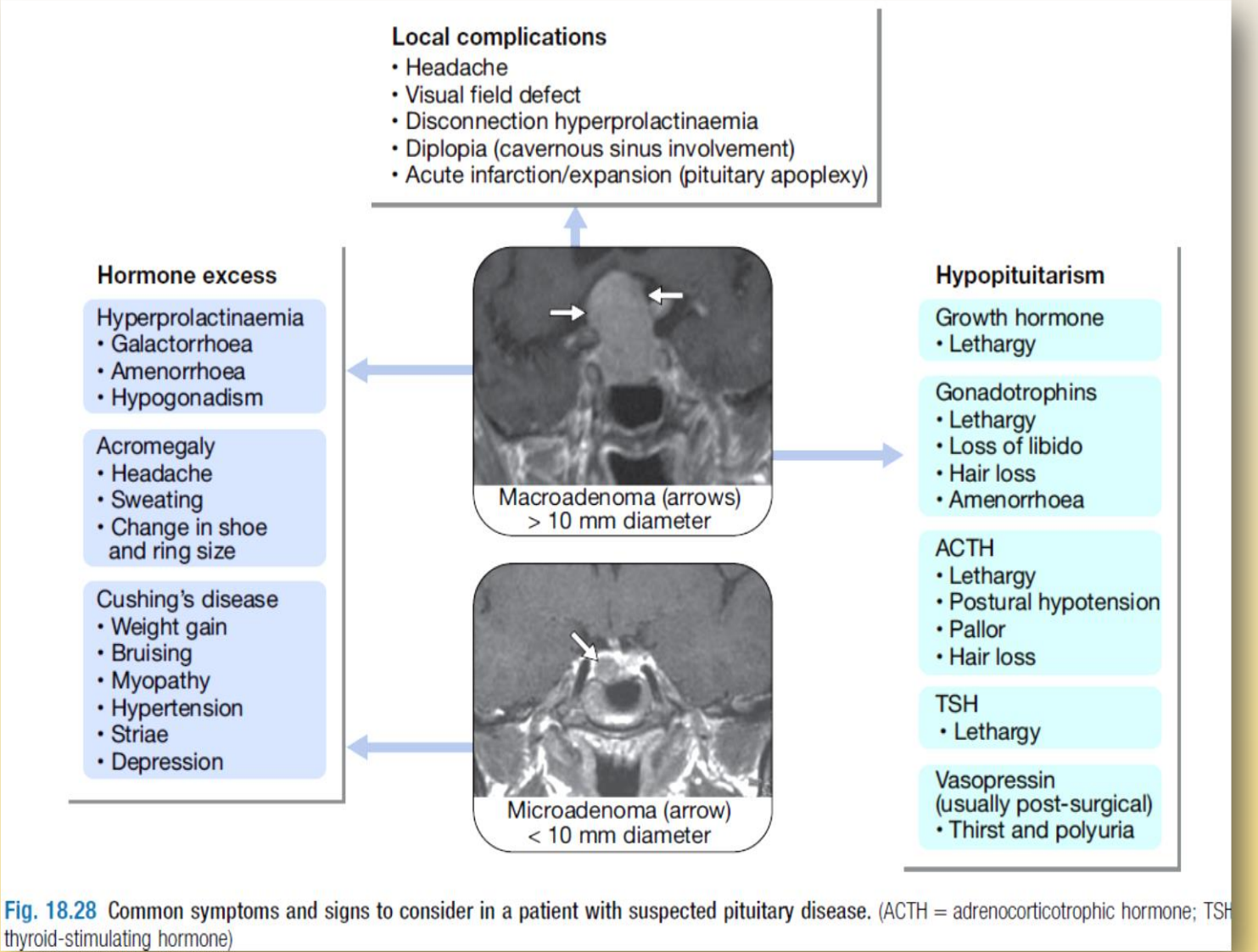


Fig. 18.28 Common symptoms and signs to consider in a patient with suspected pituitary disease. (ACTH = adrenocorticotrophic hormone; TSH thyroid-stimulating hormone)

Panhypopituitarism:

- Panhypopituitarism is a condition in which adequate production of all anterior pituitary hormones is lacking, usually because of a large tumor, apoplexy,, or complications of pituitary surgery. Patients require daily replacement of thyroxine and cortisol. Replacement of sex hormones and GH is individualized.

Investigations of hypopituitarism

- The aims of investigation of hypopituitarism are to biochemically assess the extent of pituitary hormone deficiency and also to elucidate the cause.

❑Basal hormone levels:

➢ Basal concentrations of the anterior pituitary hormone, as well as the target organ hormone, should be measured, as the pituitary hormones may remain within the normal range despite low levels of target hormone.

➢ Measurement of the pituitary hormone alone does not demonstrate that the level is inappropriately low, and the diagnosis may be missed.

- LH and FSH, and testosterone (9 a.m.) or estradiol.
- TSH and FT4.
- 9 a.m. cortisol and ACTH.
- PRL.
- IGF-1 (NB. May be normal in up to half of GHD, depending on age).

- In acutely unwell patients, the priority is to diagnose and treat cortisol deficiency. Other tests can be undertaken later.
- There is Specific dynamic tests for diagnosing hormone deficiency.
- All patients with biochemical evidence of pituitary hormone deficiency should have an MRI or CT scan to identify pituitary or hypothalamic tumors. If a tumour is not identified, then further investigations are indicated to exclude infectious or infiltrative causes.

18.43 How and when to do an ACTH stimulation test

Use

- Diagnosis of primary or secondary adrenal insufficiency
- Assessment of HPA axis in patients taking suppressive glucocorticoid therapy
- Relies on ACTH-dependent adrenal atrophy in secondary adrenal insufficiency, so may not detect acute ACTH deficiency (e.g. in pituitary apoplexy, p. 683)

Dose

- 250 μg $ACTH_{1-24}$ (Synacthen) by IM injection at any time of day

Blood samples

- 0 and 30 mins for plasma cortisol
- 0 mins also for ACTH (on ice) if Addison's disease is being considered (patient not known to have pituitary disease or to be taking exogenous glucocorticoids)

Results

- Normal subjects: plasma cortisol >500 nmol/L (approximately 18 μg/dL)* either at baseline or at 30 mins
- Incremental change in cortisol is not a criterion

*The exact cortisol concentration depends on the cortisol assay being used.
(ACTH = adrenocorticotrophic hormone; HPA = hypothalamic–pituitary–adrenal)

18.55 Tests of growth hormone secretion

GH levels are commonly undetectable, so a choice from the range of 'stimulation' tests is required:

- Insulin-induced hypoglycaemia
- Arginine (may be combined with GHRH)
- Glucagon
- Clonidine (in children)

(GH = growth hormone; GHRH = growth hormone-releasing hormone)

18.56 How and when to do an insulin tolerance test

Use

- Assessment of the HPA axis
- Assessment of GH deficiency
- Indicated when there is doubt after the other tests in Box 18.53
- Usually performed in specialist centres, especially in children
- IV glucose and hydrocortisone must be available for resuscitation

Contraindications

- Ischaemic heart disease
- Epilepsy
- Severe hypopituitarism (0800 hrs plasma cortisol < 180 nmol/L (6.6 μg/dL))

Dose

- 0.15 U/kg body weight soluble insulin IV

Aim

- To produce adequate hypoglycaemia (tachycardia and sweating with blood glucose < 2.2 mmol/L (40 mg/dL))

Blood samples

- 0, 30, 45, 60, 90, 120 mins for blood glucose, plasma cortisol and growth hormone

Results

- Normal subjects: GH > 6.7 μg/L (20 mIU/L)*
- Normal subjects: cortisol > 550 nmol/L (approximately 20.2 μg/dL)*

*The precise cut-off figure for a satisfactory cortisol and GH response depends on the assay used and so varies between centres.
(GH = growth hormone; HPA = hypothalamic–pituitary–adrenal)

Management

- Hormonal replacement & specific treatment – of underlying pathology(like pituitary macroadenoma) may be required.
- **glucocorticoid replacement therapy** consists of oral hydrocortisone 15–20 mg daily in divided doses, typically 10 mg on waking and 5 mg at around 1500 hrs. These are physiological replacement doses that should not cause Cushingoid side-effects. The dose may need to be adjusted for the individual patient. Excess weight gain usually indicates over replacement, while persistent lethargy may be due to an inadequate dose or lack of absorption. Mineralocorticoid replacement is not required.

- **Thyroid hormone replacement:** Levothyroxine 50–150 µg once daily should be given, it has a half-life of 7 days so it should always be taken as a single daily dose.
- Unlike in primary hypothyroidism, measuring TSH is not helpful in adjusting the replacement dose because patients with hypopituitarism often secrete glycoproteins that are measured in the TSH assays but are not bioactive. The aim is to maintain serum T4 in the upper part of the reference range. It is dangerous to give thyroid replacement in adrenal insufficiency without first giving glucocorticoid therapy, since this may precipitate adrenal crisis.

- **Sex hormone replacement:** This is indicated if there is gonadotrophin deficiency in women under the age of 50 and in men to restore normal sexual function and to prevent osteoporosis. Estrogen/testosterone administration is the usual method of replacement, but gonadotrophin therapy is required if fertility is desired.

- Growth hormone (GH) replacement:

➢GH is administered by daily subcutaneous self-injection.

➢Uses:

✓ In children and adolescents with GH deficiency and discontinued once the epiphyses had fused.

✓In hypopituitary adults who remain lethargic and unwell compared with a healthy population in spite of receiving full replacement with hydrocortisone, levothyroxine and sex steroids ,as some of these patients feel better, and have objective improvements in their fat: muscle mass ratio and other metabolic parameters, if they are also given GH replacement.

- ✓Treatment with GH may also help young adults to achieve a higher peak bone mineral density.
- ➢The principal side-effect is sodium retention, manifest as peripheral edema or carpal tunnel syndrome if given in excess. For this reason, GH replacement should be started at a low dose, with monitoring of the response by measurement of serum IGF-1.

Pituitary tumour

- Pituitary adenomas are the commonest pituitary tumors in adults, Pituitary carcinoma is very rare (<0.1% of all tumors) and is most commonly ACTH- or PRL-secreting.
- Incidental pituitary lesions discovered on imaging (MRI or CT scan) are called "pituitary incidentalomas.“ Most pituitary incidentalomas are benign, nonfunctional pituitary adenomas; however, a small percentage may be Rathke cleft cysts (benign embryologic remnants), craniopharyngiomas, or meningiomas. In patients with a history of malignancy, metastatic disease should be considered.

- **Classification**

❑According to Size:

✓Microadenoma <1cm.

✓Macroadenoma ≥1cm.

❑Functional status (clinical or biochemical)

✓Prolactinoma 35–40%.

✓Non-functioning 30–35%.

✓GH (acromegaly) 10–15%.

✓ACTH adenoma (Cushing's disease) 5–10%.

✓TSH adenoma <5%.

Clinical assessment of pituitary tumors

- A common but non-specific presentation is with headache, which may be the consequence of stretching of the diaphragma sellae.
- Mass effects (macroadenomas only):

✓compression of the optic chiasm classically causes bitemporal hemianopia or upper quadrantanopia, however any type of visual field defect can result from suprasellar extension of a tumour because it may compress the optic nerve (unilateral loss of acuity or scotoma)or the optic tract (homonymous hemianopia).

✓Optic atrophy

- ✓Lateral extension of a sellar mass into the cavernous sinus with subsequent compression of the 3rd, 4th or 6th cranial nerve may cause diplopia and strabismus.
- Hypopituitarism.
- Clinical features of hormonal excess.
- Occasionally, pituitary tumors infarct or there is bleeding into cystic lesions. This is termed ‘pituitary apoplexy’ and may result in sudden expansion with local compression symptoms and acute-onset hypopituitarism.

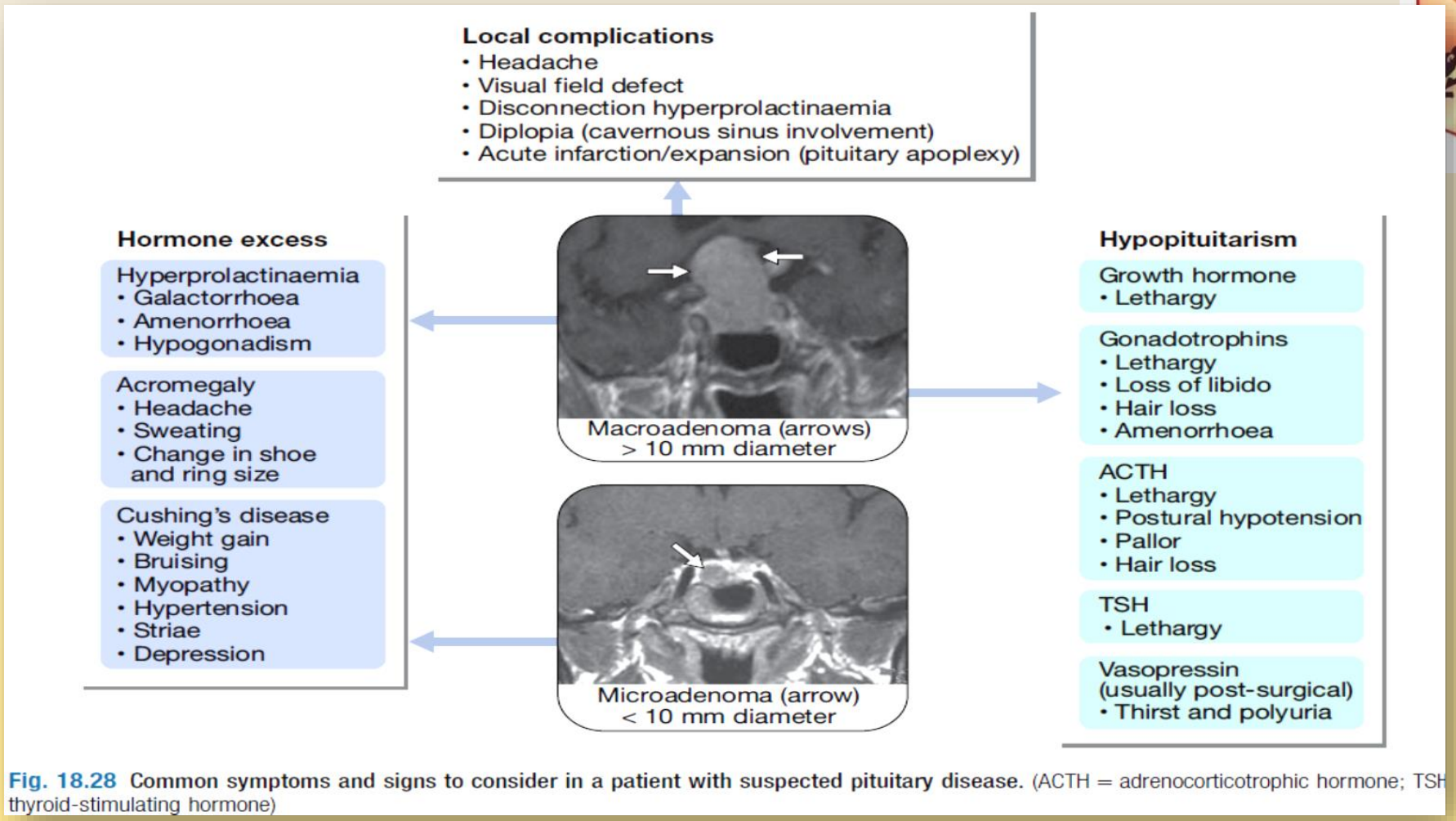


Fig. 18.28 **Common symptoms and signs to consider in a patient with suspected pituitary disease.** (ACTH = adrenocorticotrophic hormone; TSH thyroid-stimulating hormone)

Investigations

- Patients suspected of having a pituitary tumour should undergo pituitary MRI or CT.
- All patients with (para)sellar space-occupying lesions should have pituitary function assessment (assessing hormone excess/ deficiency).
- Consider visual field testing.
- the definitive diagnosis is made on histology after surgery.

Management

- **Modalities of treatment:**

❑ Surgery

❑Radiotherapy.

❑Medical therapy

Surgery

- Most operations on the pituitary are performed using the trans-sphenoidal approach via the nostrils, while transfrontal surgery via a craniotomy is reserved for suprasellar tumors and is much less frequently needed.
- It is uncommon to be able to resect lateral extensions into the cavernous sinuses, although with modern endoscopic techniques this is more feasible.

- Urgent treatment is required if there is evidence of pressure on visual pathways. The chances of recovery of a visual field defect are proportional to the duration of symptoms, with full recovery unlikely if the defect has been present for longer than 4 months.
- In the presence of a sellar mass lesion, it is crucial that serum prolactin is measured before emergency surgery is performed. If the prolactin is over 5000 mIU/L (236 ng/mL), then the lesion is likely to be a macroprolactinoma and should respond to a dopamine agonist with shrinkage of the lesion, making surgery unnecessary.

- Pituitary function should be retested 4–6 weeks following surgery, primarily to detect the development of any new hormone deficits. Rarely, the surgical treatment of a sellar lesion can result in recovery of hormone secretion that was deficient pre-operatively.
- Following surgery, usually after 3–6 months, imaging should be repeated to assess for a residual mass.

Complication of surgery

- All operations on the pituitary carry a risk of damaging normal endocrine function; this risk increases with the size of the primary lesion.

Radiotherapy

- If postsurgical imaging showed a significant residual mass and the histology confirms an anterior pituitary tumour, external radiotherapy may be given to reduce the risk of recurrence but the risk : benefit ratio needs careful individualized discussion.
- Radiotherapy is not useful in patients requiring urgent therapy because it takes many months or years to be effective and there is a risk of acute swelling of the mass.
- Stereotactic radiosurgery allows specific targeting of residual disease in a more focused fashion.

Complication of radiotherapy

- Acute swelling of the mass.
- Fractionated radiotherapy carries a life-long risk of hypopituitarism (50–70% in the first 10 years) and annual pituitary function tests are obligatory.
- There is also concern that radiotherapy might impair cognitive function, cause vascular changes and even induce primary brain tumors.

Medical therapy

- First line treatment (Dopamine agonists) in cases of Prolactinoma.
- Second line treatment in other hormonal excess adenomas.
- Hormonal replacement in presence of hypopituitarism.

Non-functioning tumors

- should be followed up by repeated imaging at intervals that depend on the size of the lesion and on whether or not radiotherapy has been administered.
- For smaller lesions that are not causing mass effects, therapeutic surgery may not be indicated and the lesion may simply be monitored by serial neuroimaging without a clear-cut diagnosis having been established.

18.57 Therapeutic modalities for functioning and non-functioning hypothalamic and pituitary tumours

	Surgery	Radiotherapy	Medical	Comment
Non-functioning pituitary macroadenoma	1st line	2nd line	–	
Prolactinoma	2nd line	2nd line	1st line Dopamine agonists	Dopamine agonists usually cause macroadenomas to shrink
Acromegaly	1st line	2nd line	2nd line Somatostatin analogues Dopamine agonists GH receptor antagonists	Medical therapy does not reliably cause macroadenomas to shrink Radiotherapy and medical therapy are used in combination for inoperable tumours
Cushing's disease	1st line	2nd line	2nd line Steroidogenesis inhibitors Pasireotide	Radiotherapy may take many years to reduce ACTH excess and medical therapies may be used as a bridge. Bilateral adrenalectomy may also be considered if the pituitary tumour is not completely resectable
Craniopharyngioma	1st line	2nd line	–	

(ACTH = adrenocorticotrophic hormone; GH = growth hormone)

References

- Davidson's Principles and Practice of Medicine/ 24th Edition 2022.
- Oxford handbook of Endocrinology and Diabetes /Fourth Edition published in 2022.
- MKSAP Endocrinology and Metabolism 19

Thanks for all