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Diagnosis of pituitary disease

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Abstract

The prevalence of pituitary disease is increasing mainly due to thbecause ofe advances in modern imaging techniques and to the an increased awareness amongst the medical community. Pituitary tumours constitute 10 –15% of all diagnosed intracranial neoplasms, and their clinical manifestations result from local mass effects (mostly neurological, visual, hypopituitarism) and/or hypersecretion. Pituitary adenomas are the most common pituitary tumours and are clinically are classified as functioning or non-functioning. The majority isMost are sporadic, but, in rare cases, they can be related with to hereditary syndromes. Other lesions involving the (para)sellar region include inflammatory and infiltrative diseases, cysts, primary or metastatic neoplasms, abscesses and internal carotid artery aneurysms. The clinical manifestations of hypopituitarism depend mainly on the type, number and severity of hormonal deficits. The Establishingment of the diagnosis requires hormonal measurements (basal or after dynamic tests), and the management includes relevant hormonal replacement and life-long monitoring.

Keywords

Craniopharyngioma; hypophysitis; hypopituitarism; pituitary adenoma; pituitary apoplexy; pituitary incidentaloma; pituitary stalk lesions; Rathke's cleft cyst

Key points

- Pituitary adenomas comprise the majority of pituitary tumours, and can be functioning or non-functioning.
- Clinical features of pituitary masses maycan result from local mass effects and/or hypersecretion.
- Sellar or parasellar masses mainly include adenomatous and non-adenomatous tumours, inflammatory and infiltrative diseases, cysts, primary or metastatic malignancies, pituitary infections and internal carotid artery aneurysms.
- All patients with pituitary masses should undergo testing for hypopituitarism, and for hormonal hypersection (in cases of pituitary adenomas), radiological assessment and neuro-ophthalmological evaluation.

Introduction (A)

The pituitary gland, or 'hypophysis cerebri', is considered to be the 'master gland' of the endocrine system, integrating, together with the hypothalamus, hormonal signals that control a plethora of endocrine and metabolic functions.

The prevalence of pituitary disease is has increasediding in over the last 10 years due tobecause of the advances in modern imaging techniques and hormonal measurements, as well as due toan the increased awareness and rate of suspicion rate for these disorders amongston the part of the medical community. Fortunately, the improvements in pituitary

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surgery and radiotherapy techniques, combined with the development of medical treatments for pituitary tumours and ~~the~~ advances in pituitary hormone replacement therapy, have led to more optimal outcomes.

Pituitary anatomy ~~(A)~~

The pituitary gland consists of ~~the~~ an anterior lobe (adenohypophysis), ~~the~~ posterior lobe (neurohypophysis)~~,~~ and ~~the~~ vestigial intermediate lobe. It lies at the base of the brain in the sella turcica, within the sphenoid bone, and is overlain by the dural sellar diaphragm, through which the pituitary stalk connects to the median eminence of the hypothalamus. The sellar diaphragm also protects the pituitary from compression by the cerebrospinal fluid (CSF). In both sides of the sella turcica, and lateral and superior to the sphenoid sinus, are the cavernous sinuses~~, in which~~; the cavernous segments of the internal carotid arteries and the cranial nerves III, IV~~,~~ and VI are located in these. The optic chiasm is anterior to the pituitary stalk, and typically sits 5~~–~~10 mm above the sellar diaphragm.

The pituitary measures approximately 13 mm transversely, 9 mm antero~~-~~posteriorly~~,~~ and 6~~–~~9 mm vertically, and in adults ~~it~~ weighs around 600 mg (range 400~~–~~900 mg). However, the size and ~~the~~ volume of the gland change in different situations~~:~~; the pituitary increases during pregnancy to almost twice its normal size, ~~whilst~~ whereas it decreases in older people.

Anterior lobe (adenohypophysis) ~~(B)~~

The anterior lobe constitutes nearly 80% of the gland's mass and comprises five hormone-secreting cell types (Table 1):

- **somatotrophs**, which produce and secrete growth hormone (GH)
- **lactotrophs**, which produce and secrete prolactin (PRL)
- **corticotrophs**, which produce and secrete adrenocorticotropic hormone (ACTH) and other pro-opiomelanocortin peptides
- **gonadotrophs**, which produce and secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH)
- **thyrotrophs**, which produce and secrete thyroid-stimulating hormone (TSH).

The anterior lobe also includes the folliculostellate cells, which are not hormone-secreting but which play an important role in the integration of information in the anterior pituitary auto/paracrine loops.

Posterior lobe (neurohypophysis) ~~(B)~~

The posterior pituitary lobe ~~is~~ comprise~~d of~~ the distal axons of the magnocellular neurosecretory cells extending from the supraoptic and paraventricular nuclei of the hypothalamus. These cells synthesize the ~~neurohypophysial~~ neurohypophyseal hormones oxytocin and vasopressin and store them in~~to~~ neurosecretory granules at their axon terminals~~;~~ ~~from where~~ they are released from here into the neurohypohyseal capillaries and ~~the~~ systemic circulation.

Blood supply ~~(B)~~

The anterior pituitary receives most of its blood supply from the hypothalamo-hypophyseal portal system, which originates from the capillary plexus of the median eminence and superior stalk, derived from the superior hypophyseal arteries. Through this system, the hypophysiotrophic hormones are delivered to the hormone-producing cells of the adenohypophysis. The remainder of the blood supply is ~~through~~ via the pituitary capsular vessels, which ~~that~~ also originate from the superior hypophyseal arteries. The posterior lobe and ~~the~~ stalk are directly supplied with blood from the hypophyseal arteries.

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-The venous drainage from both lobes is through the cavernous sinuses into the petrosal sinuses and the internal jugular veins.

Pituitary tumours (A)

Pituitary tumours constitute 10–15% of intracranial neoplasms and are often discovered incidentally on imaging performed for an unrelated reason (pituitary incidentaloma). Their clinical features maycan result from local mass effects and/or hypersecretion.[1]

The local mass effects depend on the size of the tumour and its anatomical position/ and extensions. Headache is usually the consequence of dural stretching. The neuro-ophthalmological effects include visual field defects (usually bitemporal hemianopia) from compression of the optic pathways, and ocular nerve palsies caused by lateral extension to the cavernous sinuses. Erosion of the sellar floor maycan result in sinusitis, CSF rhinorrhoea, and meningitis. The anterior pituitary hormone deficits tend to occur in a specific order, with GH and gonadotrophins affected first, followed by ACTH and TSH. PRL secretion is the most resistant, and decreased levelconcentrations indicate severe pituitary damage.

All patients with a pituitary mass should undergo testing for hypopituitarism and neuro-ophthalmological evaluation. In cases ofWith pituitary adenomas, hormonal hypersecretion needs to be assessed. Careful neuroradiology review aiming to identify imaging features helpful for the differential diagnosis is also mandatory.

Pituitary adenomas (B)

Pituitary adenomas account for 90% of pituitary tumours and have a prevalence of 77.6 cases/ per 100,000 inhabitants in the UK. They are benign lesions arising from adenohypophyseal cells and, based on their size, are classified as microadenomas (<10 mm in diameter) or macroadenomas (≥10 mm in diameter). They may hypersecrete hypophyseal hormones (functioning) or maycan be clinically non-functioning. Whilst Although mostthe majority is are sporadic, , they are in rare cases, they may be related withto hereditary syndromes, like such as multiple endocrine neoplasia type 1, Carney complex or familial/ isolated pituitary adenomas.

Non-functioning pituitary adenomas (C)

Non-functioning pituitary adenomas (NFA): these comprise 15–37% of all pituitary adenomas and have a prevalence of 7–22/ per 100,000 inhabitants. As they are not associated with hormonal hypersecretion, they usually escape early diagnosis, and are mostly recognized when they are large enough to exert pressure effects to on surrounding tissues; thus, at the time of detection, 67–90% of them are macroadenomas. Additionally, at diagnosis, 60–85% of the patients have at least one pituitary hormone deficiency.

First-line treatment for the macroadenomas is surgery, usually with theusing a trans-sphenoidal approach; this, which aims to improve or resolve the mass effects on adjacent structures, and especially the optic pathways. Radiotherapy is maycan be offered as adjuvant treatment after surgery, aiming to prevent tumour regrowth. The management of regrown non-functioning pituitary adenomas NFAs includes observation, surgery, radiotherapy or a combination of surgery and radiotherapy.

Functioning pituitary adenomas (C):

Functioning pituitary adenomasthese release excessive amounts of active hypophyseal hormones into the systemic circulation, resulting in multiple clinical manifestations. Prolactinomas are the most prevalent hormone-secreting adenomas followed by GH-producing, corticotroph, and thyrotroph adenomas. The clinical presentation, diagnosis and treatment of functioning adenomas depend on the type of hormone(s) secreted (Table 2).

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Other sellar or parasellar masses

~~(B)~~

Rathke's cleft cysts ~~(C)~~:

thesey~~~~ are benign sellar and/or suprasellar lesions that arise from remnants of Rathke's pouch.[2] Their size varies, as ~~well as~~does their content (ranging from ~~a~~ clear ~~CSF~~ CSF-like liquid to a thick mucoid material made up of cholesterol and protein). Patients with a Rathke's cleft cyst usually present with symptoms of compression ~~to~~ of adjacent structures, although incidentally detected cases are also reported. Surgery is the treatment of choice in patients with symptomatic cysts.

Other cystic lesions usually found in the suprasellar region include arachnoid, epidermoid~~,~~ and dermoid cysts.

Craniopharyngiomas: ~~(C)~~

these are sellar/parasellar tumours that arise from embryonic remnants of Rathke's pouch. They are commonly found during childhood and adolescence~~,~~.[3] ~~However, they~~but can be ~~also~~ diagnosed at any age. They are usually large masses with suprasellar extension and can invade the third ventricle and other brain structures. On imaging, craniopharyngiomas are ~~mostly~~ often predominantly cystic and usually filled with ~~a~~ cholesterol-rich fluid; purely or predominantly solid or purely cystic masses ~~can be~~are also detected. Another common finding ~~The presence of~~is calcifications inside the tumour ~~is also another common finding~~.

Patients with craniopharyngioma demonstrate many clinical features ~~due to~~resulting from local tumour effects (headache, vomiting, papilloedema, visual field deficits) and ~~due to~~ dysfunction of the hypothalamus and pituitary (obesity, problems with appetite, satiety, temperature control, hypopituitarism). Treatment of these tumours involves hypothalamus-sparing surgery followed by local radiation therapy. The long-term outcomes are not optimal ~~due to the~~because of significant morbidities.

Hypophysitis ~~(C)~~: this

~~Hypophysitis~~ is an inflammatory disease that can affect both lobes of the pituitary~~,~~ as well as the stalk. ~~The~~ Diagnosis ~~of this condition~~ can be difficult given that 50% of the cases are misdiagnosed as pituitary adenomas (Table 3).

Pituitary stalk lesions ~~(C)~~:

the spectrum ~~of pituitary stalk~~ is extensive~~,~~ but can be considered ~~and is divided in three main categories~~under three main headings:

- **neoplastic** ~~:~~: thesey~~~~ account for ~~the majority of~~most pituitary stalk lesions, with metastases (mainly from lung and breast cancer) and lymphoma being the most frequent, followed by germ cell tumors and astrocytomas~~.~~
- **inflammatory and infiltrative** ~~diseases~~ ~~:~~ hypophysitis is the most common cause, followed by neurosarcoidosis and Langerhan~~h~~s' cell histiocytosis~~.~~
- **congenital** ~~conditions~~ ~~:~~: thesey~~~~ constitute the minority of stalk lesions; pituitary hypoplasia and Rathke's cleft cyst are the most frequent causes.

Central diabetes insipidus and hyperprolactinaemia (absence of normal hypothalamic dopamine suppression of prolactin release ~~due to~~caused by stalk interruption) are the most common~~est~~ hormonal findings among~~st~~ patients with pituitary stalk lesions. Anterior hypopituitarism can also be observed. All patients should undergo clinical, biochemical~~,~~ and imaging investigations, and ~~if diagnosis remains unclear, then~~ a pituitary stalk biopsy ~~may~~can be considered if the diagnosis remains unclear.[4]

Other lesions ~~(C)~~:

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~~Other~~ less frequent sellar and ~~/~~parasellar lesions include:

- non-adenomatous tumours~~: –~~ – meningiomas (comprising ~~the majority~~most of this group), chordomas, gliomas and pituicytomas~~.~~
- pituitary infections~~: –~~ – haematogenous or local spread of infectious agents can result in pituitary abscess and perisellar arachnoiditis~~.~~
- vascular lesions~~: –~~ – internal carotid artery aneurysms, which can manifest as parasellar lesions.

Hypopituitarism ~~(A)~~

Hypopituitarism is the result of conditions that reduce or destroy ~~the~~ pituitary function or interfere with the hypothalamic secretion of pituitary-releasing hormones, leading to a complete or partial deficiency ~~in~~ of pituitary hormones.[5]

~~Etiology~~ Aetiology~~(B)~~

Apart from ~~the~~ space-occupying lesions of the pituitary, other conditions result~~ing~~ in hypopituitarism ~~include~~:

- **Vascular** ~~–:~~ pituitary apoplexy o~~i~~n the background of a pituitary tumour is the most frequent vascular cause of hypopituitarism. It can be a life-threatening condition that requires acute management (Table 4). ~~On the other hand~~In contrast, postpartum ischaemic pituitary necrosis (Sheehan's syndrome) is now relatively rare ~~due to~~because of the advances in obstetric care.
- **Traumatic** ~~–:~~ traumatic brain injury and subarachnoid haemorrhage ~~may result~~can cause ~~in~~ hypopituitarism.
- **Iatrogenic**~~: –~~ – surgery and irradiation therapy for sellar/extasellar masses or brain tumours ~~may~~can compromise pituitary function. In addition, partial hypopituitarism ~~may be seen as a result of~~can be caused various medications (glucocorticoids, opiates, etc.).
- **Congenital** ~~–:~~ ~~They can~~~~may~~these can manifest as ~~be~~ isolated deficiencies ~~due to~~caused by mutations in the genes coding for a specific hormone, or multiple deficiencies resulting from abnormal pituitary development (e.g. *PROP1*~~,~~, *HESX1*~~,~~ and *POU1F1* gene mutations).

Clinical manifestation and diagnosis ~~(B)~~

The clinical features of hypopituitarism vary and depend on the rapidity of onset, ~~the~~ severity of ~~the~~ hormonal defect(s)~~,~~ and ~~the~~ number and type of hormones affected. ~~The~~ Establishing~~ment of~~ the diagnosis requires hormonal measurements (basal or after dynamic tests) (Table 5).

Treatment ~~(B)~~

Hydrocortisone is the treatment of choice in central hypoadrenalism (usual total daily dosage ~~of~~ 15–20 mg divided into two or three doses). Patients should take the highest dose in the morning on ~~at a~~waken~~in~~g and the second in the afternoon (two-dose regimen), or the second and third at lunch~~-~~time and in the late afternoon~~,~~ respectively (three-dose regimen).

Central hypothyroidism is managed with levothyroxine in doses sufficient to achieve serum free thyroxine ~~level~~concentrations in the mid to upper half of the reference range, but ~~and~~ only after adequate hydrocortisone initiation (because thyroid hormone replacement ~~may~~can aggravate adrenal insufficiency in patients with untreated ~~steroid~~corticosteroid deficiency).

~~Males~~ Men and premenopausal females with central hypogonadism should be offered sex-steroid replacement therapy (provided there are no contraindications). Diabetes insipidus is managed with desmopressin, and GH deficiency with recombinant GH.

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Comment [CMW3]: AQ: please confirm that these doses match those recommended by the BNF.

Comment [NK4]: These are the doses mostly used in clinical practice.

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Comment [CMW5]: AQ: can 'females' include children, or is it just adult women?

Comment [NK6]: This is just premenopausal women (the statement does not apply to children)

Key references

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3. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev* 2006; **27**: 371–97.
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5. Fleseriu M, Hashim IA, Karavitaki N, et al. Hormonal replacement in hypopituitarism in adults: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2016; **101**: 3888–921.

Table 1: Hormone-producing cells in the anterior pituitary gland

Type of cell	**Percentage of cells in anterior pituitary lobe**	**Distribution of cells**
Somatotrophs	40–50%	Lateral wings of adenohypophysis
Lactotrophs	15–20%	Dispersed populations throughout the anterior lobe; mainly in the posterior part of the lateral wings
Corticotrophs	15–20%	Middle and posterior portion of anterior lobe
Gonadotrophs	10–15%	Distributed through anterior lobe
Thyrotrophs	5–10%	Anterior medial part of adenohypophysis

Table 2~~:~~ Clinical features, diagnosis and treatment of functioning pituitary adenomas

Prolactinoma
Clinical features • Females~~:~~ – galactorrhoea, hypogonadism (oligo/amenorrhoea~~, and~~ infertility) • Males~~:~~ – hypogonadism (impotence, decreased libido), galactorrhoea (very rare)
Diagnosis • Hyperprolactinaemia (after excluding~~sion of~~ macroprolactinaemia and ~~of~~ other causes of increased PRL ~~level~~concentration~~s~~) • Immunoradiometric PRL measurement at a serum dilution of 1:100 ~~in cases of~~for pituitary macroadenomas with normal or mildly elevated PRL values when the so-called 'hook effect' is suspected (high ~~level~~concentrations of circulating PRL cause~~s~~ antibody saturation in the immunoradiometric assay, leading to ~~artifactually~~ artefactually low results)
Treatment • Medical therapy with dopamine agonists (cabergoline as first~~-~~-line treatment, alternatively bromocriptine ~~alternatively~~) • Surgery if there is resistance or intolerance to medical treatment • Radiotherapy in resistant or aggressive prolactinomas, usually after surgery
GH-secreting adenomas
Clinical features • Adults~~:~~ – acromegaly (acral enlargement, prognathism, frontal bossing, soft tissue overgrowth, hyperhidrosis, arthralgias, fatigue) • Children and ~~adolescence~~adolescents~~:~~ – gigantism
Diagnosis • Serum IGF-1 ~~level~~concentrations above the age-and sex-adjusted reference range • Lack of suppression of GH ~~level~~concentrations (<0.4 µg~~/l~~/litre) during a 75 g~~r~~ oral glucose load
Treatment • Surgery • Medical therapy~~:~~ – somatostatin analogues, dopamine agonists, pegvisomant • Radiotherapy if ~~no control of the~~ disease is not controlled by surgery and medical treatment
ACTH-secreting adenomas (Cushing's disease)
Clinical features • Cushing's syndrome phenotype (weight gain and central obesity, skin thinning, purple striae, moon face, buffalo hump, proximal muscle weakness, spontaneous ecchymosis, increased supraclavicular fullness)
Diagnosis • Endogenous hypercortisolism ~~(~~established by increased 24-hour urinary~~e~~ free cortisol ~~level~~concentrations, loss of diurnal rhythm of cortisol secretion (serum~~, or~~ salivary), lack of serum cortisol suppression on overnight or ~~low~~ low-dose dexamethasone suppression test~~)~~ • Non-suppressed plasma morning~~–~~ ACTH ~~level~~concentrations

Comment [MG7]: Production Dept to cross-reference to Prolactinoma chapter from Niamh Martin

Comment [CMW8]: AQ: throughout the table: does 'Females' and 'Males' refer to all ages or just adult patients?

Comment [NK9]: These apply to adults and wherever the statement involves children, we have mentioned this.

Comment [MG10]: Production Dept to cross-reference to Acromegaly chapter from Will Drake

Comment [MG11]: Production Dept to cross-reference to Cushing's chapter from John Newell-Price

- CRH stimulation test, ~~high~~ high-dose dexamethasone suppression test, bilateral inferior petrosal sinus sampling

Treatment

- Surgery
- Radiotherapy
- Medical therapy~~:~~ – most commonly ~~used~~ with steroidogenesis inhibitors
- Bilateral adrenalectomy

TSH-secreting adenomas

Clinical features

- Hyperthyroidism

Diagnosis

- Non-suppressed TSH ~~level~~concentrations in the presence of high ~~FT4~~free T4 and~~,~~ ~~F~~free T3 concentrations
- TRH stimulation test, T3 suppression test

Treatment

- Surgery
- Medical therapy with somatostatin analogues (usually after non-curative surgery)
- Radiotherapy if ~~no control of the~~ disease is not controlled by surgery and medical treatment

Functioning gonadotroph adenomas

Clinical features

- Females~~:~~ – menstrual irregularities (oligo/amenorrhoea, spotting, menorrhagia), infertility, ovarian hyperstimulation syndrome (premenopausal women); no clinical syndrome in postmenopausal women
- Males~~:~~ – testicular enlargement, hypogonadism

Diagnosis

- Females~~:~~ – hyperoestrogenism (occasionally normal or fluctuating oestrogen ~~level~~concentrations); serum FSH ~~level~~concentrations mildly elevated or within reference range; serum LH suppressed or less often within reference range
- Males~~:~~ – serum FSH elevated; varying serum LH and testosterone ~~level~~concentrations (slightly below the reference range, normal or elevated); increased sperm count may be seen

Treatment

- Surgery combined or not with radiotherapy

In all cases, pressure effects of the adenoma ~~to~~ on surrounding structures ~~from the adenoma~~ may be seen.

CRH~~:~~ corticotrophin-releasing hormone~~,~~; ~~(PRL: prolactin, GH: growth hormone,~~ IGF-1~~:~~ insulin-like growth factor 1~~,~~; ~~ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, FF~~T3~~: free~~ triiodothyronine; T4~~: free~~ thyroxine~~,~~ ~~FSH: follicle-stimulating hormone, LH: luteinizing hormone)~~.

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Table 3~~:~~ Types, clinical features, imaging characteristics and treatment of hypophysitis

Types of hypophysitis • Lymphocytic hypophysitis~~:~~, classically in women during or after parturition • Granulomatous hypophysitis • Xanthomatous hypophysitis • IgG-4 hypophysitis~~:~~ – in patients with IgG-~~4~~ 4-related disease • Drug-induced hypophysitis (ipilimumab, nivolumab, pembrolizumab)
Clinical features • Local tumour effects (headache, visual deterioration) • Anterior hypopituitarism • Diabetes insipidus
Imaging characteristics • Symmetrical enlargement of the pituitary; stalk ~~may~~can be thickened, and suprasellar extension ~~may~~can be seen • A highly cystic lesion is often found in xanthomatous hypophysitis
Treatment • High doses of glucocorticoids (although potential ~~side e~~adverse effects should be carefully considered on an individual case basis) • Hormone replacement therapy in cases of hypopituitarism • Trans-sphenoidal surgery if visual deterioration and for histological confirmation of the diagnosis

IgG, immunoglobulin G.

Comment [CMW12]: AQ: please confirm definition is correct.

Comment [NK13]: This is correct.

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Table 4~~:~~ Pituitary apoplexy: pathophysiology, clinical presentation, differential diagnosis and management

Pathophysiology • Haemorrhage or infarction, usually on a background of a pituitary tumour • ~~Precipitating~~ Causative factors~~:~~ – hypertension, major surgery, coagulopathies, anticoagulation therapy, pregnancy, dynamic pituitary function testing, ~~and~~ head trauma
Clinical presentation • Acute severe headache that ~~may~~can be accompanied by nausea and vomiting • Ocular nerve palsies, reduced visual acuity, visual field defects (usually bitemporal hemianopia) • Meningism (fever, neck stiffness, photophobia) • Altered consciousness
Differential diagnosis • Subarachnoid haemorrhage • Meningitis (bacterial or viral) • Brainstem infarction • Cavernous sinus thrombosis
Management • Supportive measures to ensure haemodynamic stability and careful monitoring of fluid and electrolyte balance • Immediate administration of high-dose glucocorticoids, especially in haemodynamically unstable cases or with severe neurological or neuro-ophthalmological signs; this~~it~~ covers the increased risk of hypoadrenalism and has significant anti-inflammatory and anti-oedematous effects • Surgery is offered ~~in the presence of~~if there is severe visual acuity and visual field impairment (not isolated ophthalmoplegia), altered consciousness, deteriorating visual or neurological signs or of further enlargement of the sellar mass on serial imaging

Table 5~~:~~ Diagnosis of pituitary hormone deficits

GH deficiency • GH stimulation testing is mandatory (insulin tolerance test, GHRH and arginine stimulation test, glucagon stimulation test) • Normal IGF-1 ~~level~~concentrations does not exclude the diagnosis
FSH/LH deficiency • Males ~~–:~~ low morning serum testosterone ~~level~~concentrations (before 10:00 hours and ideally corrected for SHBG) and low or normal gonadotrophins • Females~~:~~ ~~–~~ – low serum oestradiol ~~level~~concentrations and low or normal gonadotrophins in the presence of oligomenorrhoea or amenorrhoea (premenopausal women); absence of high serum FSH and LH (postmenopausal women)
ACTH deficiency • Serum cortisol ~~level~~concentrations at 08:00–09:00 hours <100 nmol~~/L~~/litre (in the absence of ~~steroid~~corticosteroid administration) are indicative of adrenal insufficiency • If morning cortisol values are ~~between~~ 100~~–~~ ~~and~~ 400 nmol~~/L~~/litre, a dynamic test (e.g. insulin tolerance test, glucagon stimulation test) is required to establish the diagnosis ~~(eg. insulin tolerance test, glucagon stimulation test)~~. ~~The~~ Cut-offs for serum cortisol ~~need to~~should be defined by each laboratory, but overall peak serum cortisol >500 nmol~~/L~~/litre at 30 or 60 minutes excludes the diagnosis
Central hypothyroidism • Low free thyroxine ~~level~~concentrations in conjunction with ~~a~~ low, normal, or mildly elevated TSH in the setting of pituitary disease
Central diabetes inspidus • Confirm hypotonic polyuria – simultaneous measurement of serum/plasma and urine osmolarity in the presence of polyuria (>50 ~~mL~~ml/kg of body weight/24 hours~~*),~~[a]) • Urine osmolarity >600 mOsmol/kg~~)~~ effectively excludes the diagnosis of diabetes insipidus (urine osmolarity/plasma osmolarity ratio should be ≥2 during urine concentration); urine dipstick should be negative for glucose • Water deprivation test may also be needed

[a]~~*~~ Clinical correlation is important in this context (~~for example~~e.g., hypotonic polyuria ~~may~~can also result ~~following~~ from the infusion of large volumes of intravenous fluids).

~~(GH: growth hormone,~~ GHRH~~:~~ , growth hormone-releasing hormone~~,~~ ; IGF-1~~:~~ , insulin-like growth factor 1~~,~~ ; ~~FSH: follicle-stimulating hormone, LH: luteinizing hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone,~~ SHBG~~:~~ , sex hormone-binding globulin.~~)~~

Comment [CMW14]: AQ: Does 'Males' and 'Females' refer to all ages?

Comment [NK15]: This section refers to post-pubertal subjects. I would suggest we leave it the way it is.

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 30-year-old woman was referred to ~~Endocrinology~~ the endocrine clinic with~~for~~ a ~~one~~1-year history of headaches, amenorrhoea and decreased libido. She had no visual deterioration. ~~She had~~There was no significant past ~~medical~~ history, and she was not ~~on~~ taking any medication. ~~Hormonal workup~~Initial i

Investigations

- ~~revealed~~ Hypogonadotrophic hypogonadism~~, as well as increased~~
- Serum prolactin ~~levels (~~15,000 mU~~/L~~/litre~~, reference range~~ (60~~-~~620)~~.~~
- ~~The~~ Insulin-like growth factor 1~~IGF-1~~ and adrenocorticotrophic hormone~~ACTH~~ reserve were normal
- Thyroid function was normal ~~and there was no hypothyroidism. She had no visual deterioration.~~
- MR scan of the pituitary~~Pituitary MRI~~ revealed a macroadenoma abutting, but not compressing, the optic chiasm~~.~~

What is the best choice of treatment?

A. Dopamine agonist
B. Levothyroxine
C. Pituitary radiotherapy
D. Somatostatin analogue
E. Trans-sphenoidal adenom~~ate~~ectomy

Correct answer: A.

This patient has a macroprolactinoma. Dopamine agonists are the first-line treatment for this tumour~~,~~ as they can ~~lead to~~correct prolactin ~~normalization~~abnormalities, restore~~ation of~~ gonadal function and lead to tumour shrinkage. Surgery (E) is an alternative option for patients who show resistance or intolerance to medical treatment. Radiation therapy (C) is used only ~~in~~ for resistant or ~~/~~aggressive prolactinomas, and usually after surgery. Somatostatin analogues (D) are not effective in the treatment of prolactinomas, and levothyroxine (B) has no place in the management of this patient as there is no hypothyroidism.

Question 2

A 45-year-old man was referred to the endocrine clinic for further assessment. ~~of~~~~Endocrinology due to a 3 cm pituitary mass, which had been found on l~~imaging, performed for headaches, had shown a 3 cm pituitary mass, likely to be a pituitary adenoma, occupying the sella, with suprasellar extension and invasion of the cavernous sinuses. Th~~H~~e patient ~~had~~ reported tiredness and low libido but no polyuria or polydipsia. ~~The Nneuroradiologist reported that gy review suggested that the mass was is most likely to be a pituitary adenoma, occupying the sella with suprasellar extenstion and invasion of the cavernous sinuses.~~ There were no clinical manifestations of acromegaly, Cushing's syndrome or hyperthyroidism.

Investigations

- ~~Hormonal tests revealed~~ ~~IGF-1~~Insulin-like growth factor 1 below the reference range~~,~~
- Hypogonadotrophic hypogonadism~~,~~

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Comment [JC16]: Authors: Could we have some figures and ranges for this to simulate clinical practice and so they have to do some interpretation?

Comment [NK17]: I would suggest we leave it like this because the values of the FSH, LH and oestradiol depend on the day of the cycle. Here by mentioning amenorrhoea and hypogonadotrophic hypogonadism, we pass the message we would like to. Happy to follow your advice though if you felt this is necessary.

Comment [CMW18]: AQ: do UK report sheets use mU/L for prolactin, rather than SI units of pmol/litre?

Comment [NK19]: Yes, UK uses mU/L.

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Comment [JC20]: Author: Could we have some figures for the first two points, with reference ranges and check that the next two are realistic

Comment [NK21]: The reference range for IGF-I ranges varies between labs and assays (also affected by age) and this is why we left it like this. For the hypogonadotrophic hypogonadism, we would suggest adding 9.00 am serum testosterone and gonadotrophins below the reference range.

•~~ACTH~~ Plasma adrenocorticotropic hormone 1.8 pmol~~/L~~/litre (3.3–15.4) ~~and~~
•~~TSH~~ Serum thyroid-stimulating hormone 0.2 mU~~/L~~/litre (0.4–5.0) ~~deficiency. There was no evidence of diabetes insipidus.~~

What should be the first step in the patient's management?

A. Administer ~~D~~desmopressin
B. Growth hormone replacement therapy
C. Hydrocortisone replacement therapy
D. Levothyroxine replacement therapy
E. Testosterone replacement therapy

Correct answer: C.

In patients with anterior hypopituitarism, hydrocortisone therapy should be initiated before any other hormonal replacement. Levothyroxine (D) should be offered after adequate hydrocortisone replacement ~~is~~ has been established, as ~~otherwise,~~ levothyroxine ~~may~~can otherwise aggravate adrenal insufficiency and lead to adrenal crisis. Growth hormone (B) and sex-steroid replacement therapy (E) can be offered later (provided there are no contraindications). ~~-~~Treatment with desmopressin (A) would be indicated if there ~~was~~ were diabetes insipidus.

Comment [CMW22]: AQ: does this imply 'should only be offered after'?

Comment [NK23]: This is correct, please change the statement as you suggest.

Question 3

A 52-year-old man presented acutely with ~~was admitted to the Emergency Department with acute~~ headache, ~~fever,~~ confusion ~~-~~and complain~~ing~~ts that light hurt his eyes.~~, photophobia, and hypotension.~~ His wife ~~confirmed~~ reported a ~~12~~ 12-month history of tiredness and episodes of feeling lightheaded. ~~-~~There was no history of polydipsia or polyuria. He had a history of ~~is medical history included~~ hypertension.
On clinical examination, he was confused, with a temperature of ~~T~~ 38.0~~°~~°C, ~~HR~~heart rate 115 beats/~~min~~minute~~,~~ and ~~BP~~blood pressure 102/68 mmHg. There was n~~N~~eck stiffness ~~was identified~~ noted ~~on clinical examination. There were~~ but no signs of ocular nerve palsies. ~~The~~

Comment [JC24]: Author: Or an investigation which excludes DI

Comment [NK25]: I would not use this phrase – investigations for DI include also blood and urine tests. Here we just present the history.

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Investigations

•Cerebrospinal fluid~~SF~~ examination showed~~A lumbar puncture report revealed~~ normal ~~level~~concentration~~s~~ of ~~CSF~~ protein, ~~normal CSF:~~a plasma:~~-~~glucose ratio and no ~~presence of~~ cells. ~~CSF c~~Culture and Gram stain ~~, as~~ and ~~well as~~ –analysis for xanthochromia were negative.
•Hormonal evaluation identified ~~hypogonadotropic~~ hypogonadotrophic hypogonadism~~.~~
•Plasma adrenocorticotrophic hormone 1.6 pmol~~/L~~/litre (3.3–15.4)
•Serum thyroid-stimulating hormone 0.3 mU~~/L~~/litre (0.4–5.0) ~~ACTH and TSH deficiency. There was no evidence of diabetes insipidus.~~
•MR scan of the brain ~~Brain MRI~~ showed a large pituitary tumour with signs of haemorrhage, but no other abnormalities~~.~~

Comment [CMW26]: AQ: please clarify 'a plasma:glucose ratio'. Is some text missing?

Comment [NK27]: Please change to glucose > 60% of serum glucose

Comment [JC28]: Could there be some figures for this with normal ranges?

Comment [NK29]: As in the previous case, I would suggest we add we would suggest adding 9.00 am serum testosterone and gonadotrophins below the reference range.

What is the most likely final diagnosis?

A. Brainstem infarction
B. Cavernous sinus thrombosis
C. Meningitis
D. Pituitary apoplexy
E. Subarachnoid haemorrhage

Correct answer: D.

This patient has developed~~had a~~ pituitary apoplexy on a background of a pituitary tumour. The normal results on ~~CSF~~ cerebrospinal fluid analysis ~~results~~ exclude ~~the~~ a diagnosis of meningitis (C) and subarachnoid haemorrhage (E). The fact that no cranial nerve palsies were noted, the absence of a history of central face or paranasal sinus~~es~~ infection, and the negative findings o~~i~~n ~~the~~ MRI eliminate the possibility of cavernous sinus thrombosis (B). Finally, there were no signs o~~i~~n the MR scan~~l~~ to indicate~~ing~~ brainstem infarction (A).

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