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Diagnosis of pituitary disease

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Abstract

The prevalence of pituitary disease is increasing mainly due to the advances in modern imaging techniques and 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 classified as functioning or non-functioning. Most are sporadic, but in rare cases, they can be related with 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 establishment 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 may 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 hypersecretion (in cases of pituitary adenomas), radiological assessment and neuro-opthalmological evaluation.

Introduction

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 increasing over the last 10 years due to the advances in modern imaging techniques and hormonal measurements, as well as the increased awareness and rate of suspicion for these disorders amongst the medical community. Fortunately, the improvements in pituitary
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 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 sphenoidal 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 comprised of the distal axons of the magnocellular neurosecretory cells extending from the supraoptic and paraventricular nuclei of the hypothalamus. These cells synthesize the neurohypophysial hormones oxytocin and vasopressin and store them in neurosecretory granules at their axon terminals, from where they are released into the neurohypophyseal 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 the pituitary capsular vessels, which also originate from the superior hypophyseal arteries. The posterior lobe and the stalk are directly supplied with blood from the hypophyseal arteries.
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 may result from local mass effects and/or hypersecretion.

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 may 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 level concentrations indicate severe pituitary damage.

All patients with a pituitary mass should undergo testing for hypopituitarism and neuro-ophthalmological evaluation. In cases of 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 may be clinically non-functioning. Whilst most are sporadic, they may be related to hereditary syndromes, like multiple endocrine neoplasia type 1, Carney complex or familial isolated pituitary adenomas.

**Non-functioning pituitary adenomas (C)**

Non-functioning pituitary adenomas (NFAs) 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 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 the using a trans-sphenoidal approach: this, which aims to improve or resolve the mass effects on adjacent structures, and especially the optic pathways. Radiotherapy may be offered as an adjuvant treatment after surgery, aiming to prevent tumour regrowth. The management of regrown non-functioning pituitary adenomas NEAs includes observation, surgery, radiotherapy or a combination of surgery and radiotherapy.

**Functioning pituitary adenomas (C)**

Functioning pituitary adenomas 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).
Other sellar or parasellar masses

Rathke’s cleft cysts (C):
These are benign sellar and/or suprasellar lesions that arise from remnants of Rathke’s pouch. Their size varies, as well as their content (ranging from a clear 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 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. However, they 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 also be detected. Another common finding is the presence of calcifications inside the tumour.

Patients with craniopharyngioma demonstrate many clinical features resulting from local tumour effects (headache, vomiting, papilloedema, visual field deficits) and 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 significant morbidities.

Hypophysitis (C):
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 lesions can be considered and divided into three main categories:

- Neoplastic:
  - Neoplastic:
  - These account for the majority of 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 Langerhans’ cell histiocytosis.

- Congenital conditions:
  - These 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 stalk interruption) are the most common hormonal findings amongst patients with pituitary stalk lesions. Anterior hypopituitarism can also be observed. All patients should undergo clinical, biochemical, and imaging investigations, and if the diagnosis remains unclear, then a pituitary stalk biopsy may be considered if the diagnosis remains unclear.

Other lesions (C):
Other less frequent sellar and parasellar lesions include:

- non-adenomatous tumours: meningiomas (comprising the majority 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 pituitary hormones.5

Etiology Aetiology(B)

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

- **Vascular**: pituitary apoplexy in 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, postpartum ischaemic pituitary necrosis (Sheehan’s syndrome) is now relatively rare due to advances in obstetric care.
- **Traumatic**: traumatic brain injury and subarachnoid haemorrhage may result in hypopituitarism.
- **Iatrogenic**: surgery and irradiation therapy for sellar/extasellar masses or brain tumours may compromise pituitary function. In addition, partial hypopituitarism may be seen as a result of various medications (glucocorticoids, opiates, etc.).
- **Congenital**: they can manifest as isolated deficiencies due to mutations in the genes coding for a specific hormone, or multiple deficiencies resulting from abnormal pituitary development (e.g., PRO1, 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 establishment 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 awakening 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 concentrations in the mid to upper half of the reference range, but only after adequate hydrocortisone initiation (because thyroid hormone replacement may aggravate adrenal insufficiency in patients with untreated steroidcorticosteroid deficiency).

Males 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.
Key references


<table>
<thead>
<tr>
<th>Type of cell</th>
<th>Percentage of cells in anterior pituitary lobe</th>
<th>Distribution of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatotrophs</td>
<td>40–50%</td>
<td>Lateral wings of adenohypophysis</td>
</tr>
<tr>
<td>Lactotrophs</td>
<td>15–20%</td>
<td>Dispersed populations throughout the anterior lobe; mainly in the posterior part of the lateral wings</td>
</tr>
<tr>
<td>Corticotrophs</td>
<td>15–20%</td>
<td>Middle and posterior portion of anterior lobe</td>
</tr>
<tr>
<td>Gonadotrophs</td>
<td>10–15%</td>
<td>Distributed through anterior lobe</td>
</tr>
<tr>
<td>Thyrotrophs</td>
<td>5–10%</td>
<td>Anterior medial part of adenohypophysis</td>
</tr>
</tbody>
</table>
Table 2: Clinical features, diagnosis and treatment of functioning pituitary adenomas

<table>
<thead>
<tr>
<th>Prolactinoma</th>
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<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>• Females: -- galactorrhoea, hypogonadism (oligo/amenorrhoea and infertility)</td>
<td></td>
</tr>
<tr>
<td>• Males: -- hypogonadism (impotence, decreased libido), galactorrhoea (very rare)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>• Hyperprolactinaemia (after excluding macroprolactinaemia and other causes of increased PRL concentrations)</td>
<td></td>
</tr>
<tr>
<td>• Immunoradiometric PRL measurement at a serum dilution of 1:100 in cases of pituitary macroadenomas with normal or mildly elevated PRL values when the so-called 'hook effect' is suspected (high concentrations of circulating PRL causes antibody saturation in the immunoradiometric assay, leading to artifactual low results)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td>• Medical therapy with dopamine agonists (cabergoline as first-line treatment, alternatively bromocriptine alternatively)</td>
<td></td>
</tr>
<tr>
<td>• Surgery if there is resistance or intolerance to medical treatment</td>
<td></td>
</tr>
<tr>
<td>• Radiotherapy in resistant or aggressive prolactinomas, usually after surgery</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>GH-secreting adenomas</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>• Adults: -- acromegaly (acral enlargement, prognathism, frontal bossing, soft tissue overgrowth, hyperhidrosis, arthralgias, fatigue)</td>
<td></td>
</tr>
<tr>
<td>• Children and adolescence: -- gigantism</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>• Serum IGF-1 concentrations above the age-and sex-adjusted reference range</td>
<td></td>
</tr>
<tr>
<td>• Lack of suppression of GH concentrations (&lt;0.4 μg/litre) during a 75 g oral glucose load</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>• Surgery</td>
<td></td>
</tr>
<tr>
<td>• Medical therapy: -- somatostatin analogues, dopamine agonists, pegvisomant</td>
<td></td>
</tr>
<tr>
<td>• Radiotherapy if no control of the disease is not controlled by surgery and medical treatment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACTH-secreting adenomas (Cushing’s disease)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
</tr>
<tr>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>• Endogenous hypercortisolism (established by increased 24-hour urinary cortisol concentrations, loss of diurnal rhythm of cortisol secretion (serum, or salivary), lack of serum cortisol suppression on overnight or low-dose dexamethasone suppression test])</td>
<td></td>
</tr>
<tr>
<td>• Non-suppressed plasma morning ACTH concentrations</td>
<td></td>
</tr>
</tbody>
</table>
- CRH stimulation test, 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 levels in the presence of high free T4 and 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 levels); serum FSH levels mildly elevated or within reference range; serum LH suppressed or less often within reference range
- Males: serum FSH elevated; varying serum LH and testosterone levels (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 on surrounding structures from the adenoma may be seen.

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

<table>
<thead>
<tr>
<th>Types of hypophysitis</th>
<th>Clinical features</th>
<th>Imaging characteristics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lymphocytic hypophysitis: classically in women during or after parturition</td>
<td>• Local tumour effects (headache, visual deterioration)</td>
<td>• Symmetrical enlargement of the pituitary; stalk <em>may</em> be thickened, and suprasellar extension <em>may</em> be seen</td>
<td>• High doses of glucocorticoids (although potential side effects should be carefully considered on an individual case basis)</td>
</tr>
<tr>
<td>• Granulomatous hypophysitis</td>
<td>• Anterior hypopituitarism</td>
<td></td>
<td>• Hormone replacement therapy in cases of hypopituitarism</td>
</tr>
<tr>
<td>• Xanthomatous hypophysitis</td>
<td>• Diabetes insipidus</td>
<td>• A highly cystic lesion is often found in xanthomatous hypophysitis</td>
<td>• Trans-sphenoidal surgery if visual deterioration and for histological confirmation of the diagnosis</td>
</tr>
<tr>
<td>• IgG-4 hypophysitis in patients with IgG-4-related disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Drug-induced hypophysitis (ipilimumab, nivolumab, pembrolizumab)</td>
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*IgG, immunoglobulin G.*
### 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 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 covers the increased risk of hypoadrenalism and has significant anti-inflammatory and anti-oedematous effects
- Surgery is offered in the presence of 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

<table>
<thead>
<tr>
<th>GH deficiency</th>
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</thead>
<tbody>
<tr>
<td>• GH stimulation testing is mandatory (insulin tolerance test, GHRH and arginine stimulation test, glucagon stimulation test)</td>
</tr>
<tr>
<td>• Normal IGF-1 level concentrations does not exclude the diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FSH/LH deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Males: low morning serum testosterone level concentrations (before 10:00 hours and ideally corrected for SHBG) and low or normal gonadotrophins</td>
</tr>
<tr>
<td>• Females: low serum oestriadiol 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)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACTH deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum cortisol level concentrations at 08:00–09:00 hours &lt;100 nmol/litre (in the absence of steroid corticosteroid administration) are indicative of adrenal insufficiency</td>
</tr>
<tr>
<td>• If morning cortisol values are between 100– and 400 nmol/litre, a dynamic test (e.g. insulin tolerance test, glucagon stimulation test) is required to establish the diagnosis (e.g. insulin tolerance test, glucagon stimulation test). The cut-offs for serum cortisol need to be defined by each laboratory, but overall peak serum cortisol &gt;500 nmol/litre at 30 or 60 minutes excludes the diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low free thyroxine level concentrations in conjunction with a low, normal, or mildly elevated TSH in the setting of pituitary disease</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Central diabetes insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Confirm hypotonic polyuria — simultaneous measurement of serum/plasma and urine osmolarity in the presence of polyuria (&gt;50 mOsm/kg of body weight/24 hours)</td>
</tr>
<tr>
<td>• Urine osmolarity &gt;600 mOsm/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</td>
</tr>
<tr>
<td>• Water deprivation test may also be needed</td>
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</tbody>
</table>

*Clinical correlation is important in this context (for example, e.g. hypotonic polyuria may also result from the infusion of large volumes of intravenous fluids).*
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-year history of headaches, amenorrhoea and decreased libido. She had no visual deterioration. She had no significant past medical history, and she was not on taking any medication. Hormonal workup Initial

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 IIGF-1 and adrenocorticotrophic hormoneACTH 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 adenomectomy

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, restoration 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 due to a 3 cm pituitary mass, which had been found on 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. The patient had reported tiredness and low libido but no polyuria or polydipsia. The neuroradiologist reported that a review suggested that the mass was most likely to be a pituitary adenoma, occupying the sella with suprasellar extension 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,
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 Ddesmopressin
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 should be offered after adequate hydrocortisone replacement is established, as otherwise levothyroxine may can otherwise aggravate adrenal insufficiency and lead to adrenal crisis. Growth hormone and sex-steroid replacement therapy can be offered later (provided there are no contraindications). Treatment with desmopressin would be indicated if there was diabetes insipidus.

Question 3
A 52-year-old man presented acutely with headache, fever, confusion, and photophobia. His wife confirmed a 12-month history of tiredness and episodes of feeling lightheaded. There was no history of polydipsia or polyuria. He had a history of hypertension. On clinical examination, he was confused, with a temperature of 38.0°C, heart rate 115 beats/min, and blood pressure 102/68 mmHg. There was neck stiffness noted on clinical examination. There were no signs of ocular nerve palsies. The investigations were normal.

Investigations
• Cerebrospinal fluid examination showed normal concentrations of CSF-protein, normal CSF:plasma glucose ratio and no presence of cells. CSF culture and Gram stain were negative as analysis for xanthochromia was negative.
• Hormonal evaluation identified hypogonadotropic hypogonadotrophic hypogonadism.
• Plasma adrenocorticotropic 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 showed a large pituitary tumour with signs of haemorrhage, but no other abnormalities.

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 a pituitary apoplexy on a background of a pituitary tumour. The normal results on CSF cerebrospinal fluid analysis exclude the 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 infection, and the negative findings on the MRI eliminate the possibility of cavernous sinus thrombosis (B). Finally, there were no signs on the MR scan to indicating brainstem infarction (A).