

# UNIVERSITY OF BIRMINGHAM

## Research at Birmingham

### Diagnosis of Pituitary Disease

Karavitaki, Niki

*DOI:*

[10.1016/j.mpm.2017.05.008](https://doi.org/10.1016/j.mpm.2017.05.008)

*License:*

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

Karavitaki, N 2017, 'Diagnosis of Pituitary Disease', *Medicine*, vol. 45, no. 8, pp. 464-469.

<https://doi.org/10.1016/j.mpm.2017.05.008>

[Link to publication on Research at Birmingham portal](#)

**Publisher Rights Statement:**

Checked for eligibility: 05/06/2017

**General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

**Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

## Diagnosis of pituitary disease

Athanasios Fountas  
Niki Karavitaki

**Athanasios Fountas MD, MSc** is an Honorary Research Associate at the College of Medical and Dental Sciences, of University of Birmingham, UK. Competing interests: none declared.

Formatted: Font: Bold

**Niki Karavitaki MD, MSc, PhD, FRCP** is a Senior Clinical Lecturer in Endocrinology at the College of Medical and Dental Sciences, of University of Birmingham and an Honorary Consultant Endocrinologist at Queen Elizabeth Hospital, UK. Niki Karavitaki has received fees for speaking, funds for research and fees for consulting from Novartis, Pfizer, Merck Serono and NovoNordisk in the last 5 years.

Formatted: Font: Bold

Formatted: Font: (Default) Arial

### Abstract

The prevalence of pituitary disease is increasing mainly ~~due to the~~ because of 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 is~~ Most 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~~ Establishing ~~ingment 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 can~~ 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-ophthalmological evaluation.

Comment [CMW1]: AQ: should this be 'hypersecretion'?

Comment [NK2]: Yes, please change it to hypersecretion

### 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~~ increasing in over the last 10 years ~~due to because of the~~ advances in modern imaging techniques and hormonal measurements, as well as ~~due to an the~~ increased awareness and rate of suspicion ~~rate~~ for these disorders amongst on the part of the medical community. Fortunately, the improvements in pituitary

Formatted: Indent: First line: 1.25 cm

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.

Formatted: Font color: Blue

### **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.

Formatted: Font: Bold, Not Italic

### **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-neurohypophyseal~~ hormones oxytocin and vasopressin and store them ~~in~~ in neurosecretory granules at their axon terminals; ~~from where~~ they are released from here into the neurohypophyseal capillaries and ~~the~~ systemic circulation.

Formatted: Font: Bold, Not Italic

### **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 hypophysiotropic hormones are delivered to the hormone-producing cells of the adenohypophysis. The remainder of the blood supply is ~~through-via~~ through 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.

Formatted: Font: Bold, Not Italic

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

Formatted: Indent: First line: 1.25 cm

### **Pituitary tumours (A)**

Formatted: Font color: Blue

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.<sup>1</sup>

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 With 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)**

Formatted: Font: Bold, Not Italic

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 Although most the majority is are sporadic, they are in rare cases, they may be related with to hereditary syndromes, like such as multiple endocrine neoplasia type 1, Carney complex or familial isolated pituitary adenomas.

Formatted: Indent: First line: 0 cm

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

Formatted: Font: Bold, No underline

~~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.

Formatted: Font: Bold

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 is may can 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.

Formatted: Indent: First line: 1.25 cm

Formatted: Font: Not Bold

### **Functioning pituitary adenomas (C):**

Formatted: Font: Bold, No underline

~~Functioning pituitary adenomas~~ these 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**

~~(B)~~

Formatted: Font: Bold, Not Italic

Formatted: Font: Bold, Not Italic

### **Rathke's cleft cysts (C):**

Formatted: Font: Bold, No underline

these are benign sellar and/or suprasellar lesions that arise from remnants of Rathke's pouch.<sup>2</sup> 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~~ 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)**

Formatted: Font: Bold, No underline

Formatted: Font: Bold, No underline

these are sellar/parasellar tumours that arise from embryonic remnants of Rathke's pouch. They are commonly found during childhood and adolescence.<sup>3</sup> 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 also detected. Another common finding 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**

Formatted: Font: Bold, No underline

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).

Formatted: No underline

### **Pituitary stalk lesions (C):**

Formatted: Font: Bold, No underline

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

- **neoplastic** -: these 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 Langerhans' cell histiocytosis.
- **congenital conditions** -: these constitute the minority of stalk lesions; pituitary hypoplasia and Rathke's cleft cyst are the most frequent causes.

Formatted: Font: Bold

Central diabetes insipidus and hyperprolactinaemia (absence of normal hypothalamic dopamine suppression of prolactin release due to caused by stalk interruption) are the most commonest 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 diagnosis remains unclear, then a pituitary stalk biopsy may can be considered if the diagnosis remains unclear.<sup>4</sup>

### **Other lesions (C):**

Formatted: Font: Bold, No underline

~~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.<sup>5</sup>

Formatted: Font color: Blue

Formatted: Indent: First line: 0 cm

### **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~~ 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 by 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).

Formatted: Font: Bold, Not Italic

Formatted: Font: Bold, Not Italic

Formatted: Font: Bold

Formatted: Font: Bold

Formatted: Font: Bold

Formatted: Font: Bold

Formatted: Font: Not Italic

### **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).

Formatted: Font: Bold, Not Italic

### **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~~ 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 ~~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.

Formatted: Font: Bold, Not Italic

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.

Formatted: Indent: First line: 1.25 cm

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

1. Freda PU, Beckers AM, Katznelson L, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2011; **96**: 894–904.
2. Trifanescu R, Ansorge O, Wass JA, Grossman AB, Karavitaki N. Rathke's cleft cysts. *Clin Endocrinol (Oxf)* 2012; **76**: 151–60.
3. Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev* 2006; **27**: 371–97.
4. Catford S, Wang YY, Wong R. Pituitary stalk lesions: systematic review and clinical guidance. *Clin Endocrinol (Oxf)* 2016; **85**: 507–21.
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

<b>Prolactinoma</b>
<p><i>Clinical features</i></p> <ul style="list-style-type: none"> <li>Females: galactorrhoea, hypogonadism (oligo/amenorrhoea and infertility)</li> <li>Males: hypogonadism (impotence, decreased libido), galactorrhoea (very rare)</li> </ul>
<p><i>Diagnosis</i></p> <ul style="list-style-type: none"> <li>Hyperprolactinaemia (after exclusion of macroprolactinaemia and other causes of increased PRL level concentrations)</li> <li>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 causes antibody saturation in the immunoradiometric assay, leading to artifactually artefactually low results)</li> </ul>
<p><i>Treatment</i></p> <ul style="list-style-type: none"> <li>Medical therapy with dopamine agonists (cabergoline as first-line treatment, alternatively bromocriptine alternatively)</li> <li>Surgery if there is resistance or intolerance to medical treatment</li> <li>Radiotherapy in resistant or aggressive prolactinomas, usually after surgery</li> </ul>
<b>GH-secreting adenomas</b>
<p><i>Clinical features</i></p> <ul style="list-style-type: none"> <li>Adults: acromegaly (acral enlargement, prognathism, frontal bossing, soft tissue overgrowth, hyperhidrosis, arthralgias, fatigue)</li> <li>Children and adolescence/adolescents: gigantism</li> </ul>
<p><i>Diagnosis</i></p> <ul style="list-style-type: none"> <li>Serum IGF-1 level concentrations above the age- and sex-adjusted reference range</li> <li>Lack of suppression of GH level concentrations (&lt;0.4 µg/litre) during a 75 g oral glucose load</li> </ul>
<p><i>Treatment</i></p> <ul style="list-style-type: none"> <li>Surgery</li> <li>Medical therapy: somatostatin analogues, dopamine agonists, pegvisomant</li> <li>Radiotherapy if no control of the disease is not controlled by surgery and medical treatment</li> </ul>
<b>ACTH-secreting adenomas (Cushing's disease)</b>
<p><i>Clinical features</i></p> <ul style="list-style-type: none"> <li>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)</li> </ul>
<p><i>Diagnosis</i></p> <ul style="list-style-type: none"> <li>Endogenous hypercortisolism (established by increased 24-hour urinary free cortisol level concentrations, loss of diurnal rhythm of cortisol secretion (serum, or salivary), lack of serum cortisol suppression on overnight or low-dose dexamethasone suppression test)</li> <li>Non-suppressed plasma morning ACTH level concentrations</li> </ul>

**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

<ul style="list-style-type: none"> <li>CRH stimulation test, <del>high-high</del> dose dexamethasone suppression test, bilateral inferior petrosal sinus sampling</li> </ul>
<p><i>Treatment</i></p> <ul style="list-style-type: none"> <li>Surgery</li> <li>Radiotherapy</li> <li>Medical therapy: <del>–</del> most commonly <del>used-with</del> steroidogenesis inhibitors</li> <li>Bilateral adrenalectomy</li> </ul>
<p><b>TSH-secreting adenomas</b></p>
<p><i>Clinical features</i></p> <ul style="list-style-type: none"> <li>Hyperthyroidism</li> </ul>
<p><i>Diagnosis</i></p> <ul style="list-style-type: none"> <li>Non-suppressed TSH <del>levelconcentrations</del> in the presence of high <del>FT4free T4 and Ffree T3</del> concentrations</li> <li>TRH stimulation test, T3 suppression test</li> </ul>
<p><i>Treatment</i></p> <ul style="list-style-type: none"> <li>Surgery</li> <li>Medical therapy with somatostatin analogues (usually after non-curative surgery)</li> <li>Radiotherapy if <del>no control of the</del> disease <del>is not controlled</del> by surgery and medical treatment</li> </ul>
<p><b>Functioning gonadotroph adenomas</b></p>
<p><i>Clinical features</i></p> <ul style="list-style-type: none"> <li>Females: <del>–</del> menstrual irregularities (oligo/amenorrhoea, spotting, menorrhagia), infertility, ovarian hyperstimulation syndrome (premenopausal women); no clinical syndrome in postmenopausal women</li> <li>Males: <del>–</del> testicular enlargement, hypogonadism</li> </ul>
<p><i>Diagnosis</i></p> <ul style="list-style-type: none"> <li>Females: <del>–</del> hyperoestrogenism (occasionally normal or fluctuating oestrogen <del>levelconcentrations</del>); serum FSH <del>levelconcentrations</del> mildly elevated or within reference range; serum LH suppressed or less often within reference range</li> <li>Males: <del>–</del> serum FSH elevated; varying serum LH and testosterone <del>levelconcentrations</del> (slightly below the reference range, normal or elevated); increased sperm count may be seen</li> </ul>
<p><i>Treatment</i></p> <ul style="list-style-type: none"> <li>Surgery combined or not with radiotherapy</li> </ul>

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: adrenocorticotrophic hormone, TSH: thyroid-stimulating hormone, FT3: ~~–~~ free triiodothyronine; T4: ~~–~~ free thyroxine, FSH: follicle stimulating hormone, LH: luteinizing hormone); ~~–~~

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

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

<b>Types of hypophysitis</b> <ul style="list-style-type: none"><li>• Lymphocytic hypophysitis: <del>is</del> classically in women during or after parturition</li><li>• Granulomatous hypophysitis</li><li>• Xanthomatous hypophysitis</li><li>• IgG-4 hypophysitis: <del>is</del> in patients with IgG-4-related disease</li><li>• Drug-induced hypophysitis (ipilimumab, nivolumab, pembrolizumab)</li></ul>
<b>Clinical features</b> <ul style="list-style-type: none"><li>• Local tumour effects (headache, visual deterioration)</li><li>• Anterior hypopituitarism</li><li>• Diabetes insipidus</li></ul>
<b>Imaging characteristics</b> <ul style="list-style-type: none"><li>• Symmetrical enlargement of the pituitary; stalk <del>may</del> be thickened, and suprasellar extension <del>may</del> be seen</li><li>• A highly cystic lesion is often found in xanthomatous hypophysitis</li></ul>
<b>Treatment</b> <ul style="list-style-type: none"><li>• High doses of glucocorticoids (although potential <del>side-e</del>adverse effects should be carefully considered on an individual case basis)</li><li>• Hormone replacement therapy in cases of hypopituitarism</li><li>• Trans_sphenoidal surgery if visual deterioration and for histological confirmation of the diagnosis</li></ul>

IgG, immunoglobulin G.

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

**Comment [NK13]:** This is correct.

**Formatted:** Font: Not Bold

**Formatted:** Font: Not Bold

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

<b>Pathophysiology</b> <ul style="list-style-type: none"><li>• Haemorrhage or infarction, usually on a background of a pituitary tumour</li><li>• <del>Precipitating-Causative</del> factors: – hypertension, major surgery, coagulopathies, anticoagulation therapy, pregnancy, dynamic pituitary function testing, <del>and</del> head trauma</li></ul>
<b>Clinical presentation</b> <ul style="list-style-type: none"><li>• Acute severe headache that <del>may</del>can be accompanied by nausea and vomiting</li><li>• Ocular nerve palsies, reduced visual acuity, visual field defects (usually bitemporal hemianopia)</li><li>• Meningism (fever, neck stiffness, photophobia)</li><li>• Altered consciousness</li></ul>
<b>Differential diagnosis</b> <ul style="list-style-type: none"><li>• Subarachnoid haemorrhage</li><li>• Meningitis (bacterial or viral)</li><li>• Brainstem infarction</li><li>• Cavernous sinus thrombosis</li></ul>
<b>Management</b> <ul style="list-style-type: none"><li>• Supportive measures to ensure haemodynamic stability and careful monitoring of fluid and electrolyte balance</li><li>• Immediate administration of high-dose glucocorticoids, especially in haemodynamically unstable cases or with severe neurological or neuro-<del>ophthalmological</del> signs; <del>this</del> covers the increased risk of hypoadrenalism and has significant anti-inflammatory and anti-oedematous effects</li><li>• Surgery is offered <del>in the presence of if there is</del> 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</li></ul>

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

<p><b>GH deficiency</b></p> <ul style="list-style-type: none"> <li>GH stimulation testing is mandatory (insulin tolerance test, GHRH and arginine stimulation test, glucagon stimulation test)</li> <li>Normal IGF-1 <del>level</del><u>concentration</u>s does not exclude the diagnosis</li> </ul>
<p><b>FSH/LH deficiency</b></p> <ul style="list-style-type: none"> <li><del>Males</del><u>—</u>: low morning serum testosterone <del>level</del><u>concentration</u>s (before 10:00 <del>hours</del><u> </u> and ideally corrected for SHBG) and low or normal gonadotroph<u>ins</u></li> <li>Females:<del>—</del><u> </u> low serum oestradiol <del>level</del><u>concentration</u>s and low or normal gonadotroph<u>ins</u> in the presence of oligomenorrhoea or amenorrh<u>oea</u> (premenopausal women); absence of high serum FSH and LH (postmenopausal women)</li> </ul>
<p><b>ACTH deficiency</b></p> <ul style="list-style-type: none"> <li>Serum cortisol <del>level</del><u>concentration</u>s at 08:00–09:00 <del>hours</del><u> </u> &lt;100 nmol/<del>L</del><u>/litre</u> (in the absence of <del>steroid</del><u>corticosteroid</u> administration) are indicative of adrenal insufficiency</li> <li>If morning cortisol values are <del>between 100 and</del><u> </u> 400 nmol/<del>L</del><u>/litre</u>, a dynamic test (<del>e.g. insulin tolerance test, glucagon stimulation test</del><u> </u>) is required to establish the diagnosis (<del>e.g. insulin tolerance test, glucagon stimulation test</del><u> </u>). <del>The</del><u> </u> Cut-offs for serum cortisol <del>need to</del><u>should</u> be defined by each lab<u>oratory</u>, but overall peak serum cortisol &gt;500 nmol/<del>L</del><u>/litre</u> at 30 or 60 minutes excludes the diagnosis</li> </ul>
<p><b>Central hypothyroidism</b></p> <ul style="list-style-type: none"> <li>Low free thyroxine <del>level</del><u>concentration</u>s in conjunction with <del>a</del><u> </u> low, normal, or mildly elevated TSH in the setting of pituitary disease</li> </ul>
<p><b>Central diabetes insipidus</b></p> <ul style="list-style-type: none"> <li>Confirm hypotonic polyuria – simultaneous measurement of serum/plasma and urine osmolarity in the presence of polyuria (&gt;50 <del>mL</del><u>ml</u>/kg of body weight/24 hours<del>*)</del><u> </u>)</li> <li>Urine osmolarity &gt;600 mOsmol/kg<del>)</del><u> </u> 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</li> <li>Water deprivation test may also be needed</li> </ul>

**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.

**Formatted:** Superscript

<sup>a\*</sup> 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.)~~ 

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

**Formatted:** Font: Not Italic

## 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 one1-year history of headaches, amenorrhoea and decreased libido. She had no visual deterioration. She hadThere was no significant past medical history, and she was not on taking any medication. Hormonal workupInitial i

#### Investigations

- ~~revealed~~ Hypogonadotropic hypogonadism, ~~as well as increased~~
- Serum prolactin levels (15,000 mU/L/litre, reference range (60–620).
- The Insulin-like growth factor 1IGF-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 pituitaryPituitary MRI revealed a macroadenoma abutting, but not compressing, the optic chiasm.

#### What is the best choice of treatment?

- Dopamine agonist
- Levothyroxine
- Pituitary radiotherapy
- Somatostatin analogue
- Trans-sphenoidal adenomeatectomy

#### 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. ofEndocrinology 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 gy 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,
- Hypogonadotropic hypogonadism,

Formatted: Font: Bold

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 hypogonadotropic 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.

Formatted: Font: Bold

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 hypogonadotropic hypogonadism, we would suggest adding 9.00 am serum testosterone and gonadotrophins below the reference range.

- ~~ACTH Plasma adrenocorticotrophic 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?

- Administer ~~D~~ desmopressin
- Growth hormone replacement therapy
- Hydrocortisone replacement therapy
- Levothyroxine replacement therapy
- 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 complainings 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  $\neq 38.0^{\circ}\text{C}$ , ~~HR~~ heart rate 115 beats/min/minute, and ~~BP~~ blood pressure 102/68 mmHg. There was ~~n~~ neck 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.

Formatted: Superscript

Formatted: Font: Bold

### Investigations

- ~~Cerebrospinal fluid~~ SF examination showed ~~A lumbar puncture report revealed~~ normal level/concentrations of CSF-protein, ~~normal CSF: a plasma: glucose ratio~~ and ~~no presence of~~ cells. ~~CSF-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?

- Brainstem infarction
- Cavernous sinus thrombosis
- Meningitis
- Pituitary apoplexy
- 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 sinuses infection, and the negative findings ~~o~~in the MRI eliminate the possibility of cavernous sinus thrombosis (B). Finally, there were no signs ~~o~~in the MR ~~scan~~ ~~to~~ indicate ~~ing~~ brainstem infarction (A).

Formatted: Left

Formatted: List Paragraph

Formatted: Normal, Left, Line  
spacing: single