Hypopituitarism

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Incidence and prevalence of hypopituitarism are estimated to be 4·2 per 100 000 per year and 45·5 per 100 000, respectively. Although the clinical symptoms of this disorder are usually unspecific, it can cause life-threatening events and lead to increased mortality. Current research has refined the diagnosis of hypopituitarism. Identification of growth hormone and corticotropin deficiency generally requires a stimulation test, whereas other deficiencies can be detected by basal hormones in combination with clinical judgment. Newly developed formulations of replacement hormones are convenient and physiological. Work has shown that many patients with brain damage—such as traumatic brain injury or aneurysmal subarachnoid haemorrhage—are at high risk of (sometimes unrecognised) hypopituitarism. Thus, a much increased true prevalence of this disorder needs to be assumed. As a result, hypopituitarism is not a rare disease and should be recognised by the general practitioner.

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Pituitary insufficiency was the topic of a 1998 *Lancet* seminar.[1] Since then, new insights in the areas of epidemiology, diagnosis, and treatment of hypopituitarism have taken place that deserve to be summarised in a current seminar.

Hypopituitarism, first described clinically by Simmonds in 1914,[2] is the inability of the pituitary gland to provide sufficient hormones adapted to the needs of the organism. It might be caused by either an inability of the gland itself to produce hormones or an insufficient supply of hypothalamic-releasing hormones. Figure 1 shows how changes in hormones that regulate pituitary and hypothalamic function might lead to hypopituitarism. Generally, hypopituitarism is chronic and lifelong, unless successful surgery or medical treatment of the underlying disorder can restore pituitary function. Patients with hypopituitarism have increased mortality.[3–5]

Causes and epidemiology

As far as we know, only one population-based study has assessed the incidence and prevalence of hypopituitarism.[6] These researchers noted a prevalence of 45·5 cases per 100 000 in a Spanish population. Incidence was 4·2 cases per 100 000 per year and increased with age. The causes of hypopituitarism were pituitary tumorous (61%), non-pituitary lesions (9%), and non-cancerous causes (30%), including 11% idiopathic cases.[6] Other disorders that classically have been regarded as rare causes of hypopituitarism include perinatal insults, genetic causes, or trauma.[1] The panel summarises causes of hypopituitarism.

Since the beginning of the 21st century, the importance of brain damage attributable to traumatic brain injury,[7] aneurysmal subarachnoid haemorrhage,[7] ischaemic stroke,[8] neurosurgery,[9] and cranial irradiation[10] as a major and formerly underestimated cause of hypothalamic-pituitary dysfunction has been highlighted. Ten systematic studies of endocrine function in a total of 749 patients in the chronic phase after admission for traumatic brain injury (most patients were studied at least 6 months after trauma)[11–20] and five studies of 122 individuals with aneurysmal subarachnoid haemorrhage[11,21–24] have been published. Tables 1 and 2 summarise the results. Taken together, 35% and 48% of the investigated patients were diagnosed with some degree of hypopituitarism after traumatic brain injury and subarachnoid haemorrhage, respectively. In most individuals, only single pituitary axes were affected. Pituitary irradiation is a well-known cause of hypopituitarism.[25] Findings of a study of patients irradiated for brain tumours distant from the hypothalamo-pituitary axis showed that 41% developed hypopituitarism.[10] In individuals undergoing surgery for non-pituitary brain tumours and in those with ischaemic stroke, rates of hypopituitarism were 38% and 19%, respectively.[8,9]

To date, traumatic brain injury and subarachnoid haemorrhage have been best characterised as causes of hypopituitarism. Respective incidences of these disorders leading to admission are 80 and 10 cases per 100 000 per year.[26,27] The estimated overall incidence of traumatic brain injury in Europe is even higher than these values, at 235 cases per 100 000 per year.[28] Application of the above-mentioned frequencies of hypopituitarism to these incidences would result in an estimated incidence of 31 cases of hypopituitarism attributable to traumatic brain injury and subarachnoid haemorrhage per 100 000 per year, when using the most conservative data. This number might still be an overestimate because of possible preselection of severely traumatised patients or varying definitions of pituitary

Search strategy and selection criteria

We searched Medline with the main search term "hypopituitarism" in combination with "epidemiology", "diagnosis", or "treatment". We further combined these terms with "hypocortisolism", "hypothyroidism", "hypogonadism", or "growth hormone deficiency". We largely selected articles from 1998 to 2006 but did not exclude frequently referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with further details and references than this Seminar has room for. The contents of this article are based on reviewed published work, our clinical and scientific judgment, and on feedback from peer reviewers.

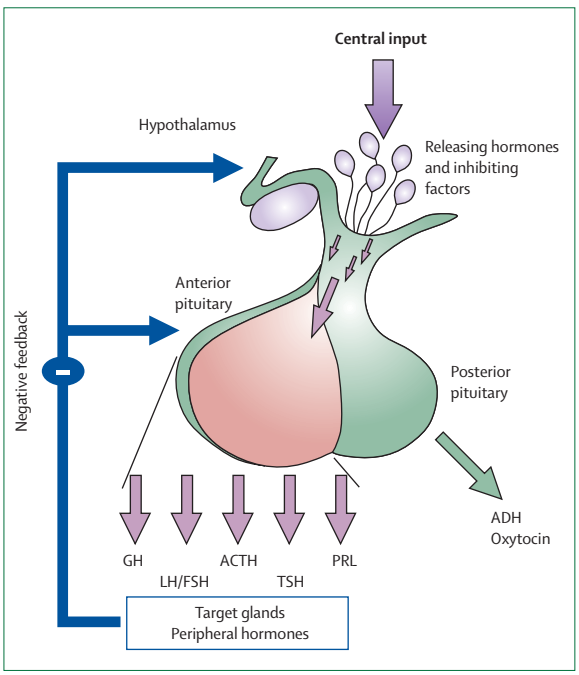

Figure 1: **Regulation of hypothalamic-pituitary-peripheral function**
The anterior pituitary produces adrenocorticotropic hormone (ACTH), thyrotropic hormone (TSH), luteinising hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), and growth hormone (GH). Their secretion is regulated by hypothalamic releasing and inhibiting factors and by negative feedback inhibition of their peripheral hormones. The posterior pituitary is a storage organ for the hypothalamic hormones antidiuretic hormone (ADH) and oxytocin. Hypopituitarism can arise at hypothalamic, stalk or pituitary level.

dysfunction used in the studies mentioned above. However, without doubt, a large amount of hypopituitarism related to brain damage remains undiagnosed. Patients with brain pathological disorders have many somatic, psychiatric, and neurological symptoms[29] that could well mask the typically subtle signs of hypopituitarism. Additionally, clinicians who treat these patients have very little awareness of this risk, and endocrine assessment is usually not considered after brain damage.[30,31]

Pathophysiology

The pituitary gland is supplied with blood by branches of the internal carotid artery. These vessels form a capillary plexus in the region of the median eminence of the hypothalamus. Blood from this area reaches the anterior pituitary by means of long and short portal veins via the pituitary stalk. The middle and inferior hypophyseal arteries supply the pituitary stalk and neurohypophysis with arterial blood. However, the anterior lobe is not included in this arterial blood supply; it is provided with oxygenated blood only through the internal and external plexus of the median eminence.[32]

The pathophysiology of hypopituitarism is dependent on the cause of the disorder and is not understood completely in some cases. For pituitary adenomas, mechanical compression of portal vessels and the pituitary stalk, and ischaemic necrosis of portions of the anterior lobe, have been postulated to be the predominant mechanism causing hypopituitarism. Moreover, increases in intrasellar pressure have been recorded in patients with pituitary macroadenomas, which could be the cause of reduced blood flow through the portal vessels and the pituitary stalk, resulting in diminished delivery of hypothalamic hormones to the anterior pituitary.[33] Empty sella is caused by herniation of the subarachnoid space and associated with flattening of the pituitary gland. This process is sometimes, but not necessarily, accompanied by hypopituitarism.[34]

The pathway by which radiation induces hypopituitarism is largely unresolved. Sparse data favour

Panel: **Causes of hypopituitarism**

Brain damage*
- Traumatic brain injury
- Subarachnoid haemorrhage
- Neurosurgery
- Irradiation
- Stroke

Pituitary tumours*
- Adenomas
- Others

Non-pituitary tumours
- Craniopharyngiomas
- Meningiomas
- Gliomas
- Chordomas
- Ependymomas
- Metastases

Infections
- Abscess
- Hypophysitis
- Meningitis
- Encephalitis

Infarction
- Apoplexia
- Sheehan's syndrome

Autoimmune disorders
- Lymphocytic hypophysitis

Haemochromatosis, granulomatous diseases, histiocytosis

Empty sella

Perinatal insults

Pituitary hypoplasia or aplasia

Genetic causes

Idiopathic causes

*Pituitary tumours are classically the most common cause of hypopituitarism. However, new findings imply that causes related to brain damage might outnumber pituitary adenomas in causing hypopituitarism.

	n	Any degree of hypopituitarism	Multiple deficiencies	GH	LH/FSH	ACTH	TSH	Remarks
Kelly et al, 2000[11]	22	8	3	4	4	1	1	
Lieberman et al, 2001[14]	70	48	12	7	2	32	15	32 patients with low morning cortisol; only 5 patients with cortisol <500 nmol/L after ACTH stimulation
Bondanelli et al, 2004[15]	50	27	6	4	7	0	5	No stimulation test for ACTH
Agha et al, 2004[12]	102	29	6	11	12	13	1	
Popovic et al, 2004[16]	67	23	7	10	6	5	3	
Aimaretti et al, 2005[13]	70	16	7	14	8	4	5	No stimulation test for ACTH
Leal-Cerro et al, 2005[17]	170	42	15	6	29	11	10	Endocrine testing only if clinical suspicion of hypopituitarism (n=99)
Schneider et al, 2006[18]	70	25	3	7	14	6	2	
Tanriverdi et al, 2006[19]	52	26	5	17	4	10	3	
Herrmann et al, 2006[20]	76	18	5	6	13	2	2	
Total (%)	749 (100)	262 (35)	69 (9)	86 (11)	99 (13)	84 (11)	47 (6)	

LH=luteinising hormone. FSH=follicle-stimulating hormone. GH=growth hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone.

Table 1: **Hypopituitarism in the chronic phase after traumatic brain injury**

	n	Any degree of hypopituitarism	Multiple deficiencies	GH	LH/FSH	ACTH	TSH	Remarks
Kelly et al, 2000[11]	2	2	0	2	0	0	0	
Brandt et al, 2004[21]	10	5	0	1	4	0	0	
Aimaretti et al, 2004[24]	40	15	4	10	5	1	3	No stimulation test for ACTH
Kreitschmann-Andermahr et al, 2004[23]	40	22	3	8	0	16	1	
Dimopoulou et al, 2004[22]	30	14	4	11	4	3	2	No stimulation test for GH (11 patients low IGF-I)
Total (%)	122 (100)	58 (48)	11 (9)	32 (26)	13 (11)	20 (16)	6 (5)	

LH=luteinising hormone. FSH=follicle-stimulating hormone. GH=growth hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone.

Table 2: **Hypopituitarism after subarachnoid haemorrhage**

direct neuronal rather than vascular damage to the hypothalamus—which is assumed to be more radiosensitive than the pituitary gland itself—as one causal factor.[35] Moreover, findings of a study undertaken in children suggest that hypothalamic dysfunction after external-beam radiotherapy is also secondary to altered neurotransmitter input from other brain centres.[36] These factors might also have a role in other forms of brain damage associated with neuroendocrine dysfunction, such as stroke, neurosurgery, or traumatic brain injury.

Traumatic brain injury and subarachnoid haemorrhage have long been known to cause lesions in the hypothalamic-pituitary region, as shown by findings of several neuropathological studies.[37–42] Haemorrhage, necrosis, and fibrosis of the pituitary gland and hypothalamus have been recorded. Stalk lesions can produce anterior-lobe infarction by damaging the portal blood supply.[42] Hypothalamic lesions were noted in two-thirds of patients who died shortly after aneurysmal subarachnoid haemorrhage,[8] consisting of areas of ischaemic necrosis, macrohaemorrhages, and microhaemorrhages.

Development of the pituitary gland is regulated by a complex interplay of several transcription factors, including HESX1, LHX1, PROP1, and POU1F1 (formerly PIT1). Mutations of these and other factors could cause pituitary malformation and hypopituitarism that might be accompanied by specific clinical symptoms.[43]

Diagnosis

Clinical presentation

Sometimes, signs and symptoms of underlying diseases accompany hypopituitarism. Tumoral masses in the sellar region with suprasellar extension can become manifest with visual impairment that is slowly progressive in most cases. Visual-field defects can present not only as classic bitemporal hemianopsia but also unilaterally in many cases. Usually, such defects remain unrecognised by patients until diagnosed by a doctor. Headaches can be an unspecific symptom of tumour masses. In case of lateral extension, rarely, signs of oculomotor nerve impairment and, even less common, additional damage to other cranial nerves within the cavernous sinus might arise. Brain damage can cause

neurological deficits, weight changes, depression, sleep disturbances, and loss of drive.

Hypopituitarism can be subclinical, indicated only by measurement of hormones, or its clinical onset might be acute and severe, necessitating admission and intensive-care management. Shortages of adrenocorticotropic hormone (ACTH),[44] thyroid-stimulating hormone (TSH),[45,46] and antidiuretic hormone (ADH)[47] are potentially life-threatening and, thus, require particular attention to warrant timely diagnosis and hormone replacement. Gonadotropin and growth-hormone deficiencies, on the other hand, cause chronic morbidity. Raised prolactin concentrations sometimes accompany hypopituitarism because of disruption of inhibitory signals by the hypothalamus. This alteration can cause lactation, tenderness of the breast, and suppression of gonadotropins, leading to symptoms of hypogonadism. Table 3 summarises clinical features of hypopituitarism.

Imaging

Cranial MRI should be done to exclude tumours and other lesions of the sellar and parasellar region after hypopituitarism has been confirmed. Of sellar tumours, the pituitary adenoma is the most frequent (figure 2). Careful review of high-resolution native and contrast-enhanced images is needed so that small lesions are not missed—eg, microadenomas (<10 mm). With MRI depicting the relation of tumours to adjacent vessels and the optic chiasm, it has a major role in presurgical planning. Traumatic damage can present with pituitary-stalk deviation, with signal inhomogeneity attributable to haemorrhage or infarction, or as empty sella (figure 2).[7] However, hypopituitarism is not excluded by normal MRI of the sellar and parasellar region.

	Investigative findings
Corticotropin deficiency	..
Chronic: fatigue, pallor, anorexia, weight loss	Hypoglycaemia, hypotension, anaemia, lymphocytosis, eosinophilia, hyponatraemia
Acute: weakness, dizziness, nausea, vomiting, circulatory collapse, fever, shock	..
Children: delayed puberty, failure to thrive	..
Thyrotropin deficiency	..
Tiredness, cold intolerance, constipation, hair loss, dry skin, hoarseness, cognitive slowing	Weight gain, bradycardia, hypotension
Children: retarded development, growth retardation	..
Gonadotropin deficiency	..
Women: oligoamenorrhea, loss of libido, dyspareunia, infertility	Osteoporosis
Men: loss of libido, impaired sexual function, mood impairment, loss of facial, scrotal, and trunk hair	Decreased muscle mass, osteoporosis, anaemia
Children: delayed puberty	..
Growth hormone deficiency	..
Decreased muscle mass and strength, visceral obesity, fatigue, decreased quality of life, impairment of attention and memory	Dyslipidaemia, premature atherosclerosis
Children: growth retardation	..
Antidiuretic hormone deficiency	..
Polyuria, polydipsia	Decreased urine osmolality, hypernatraemia, polyuria

Table 3: **Clinical features and investigative findings of hypopituitarism**

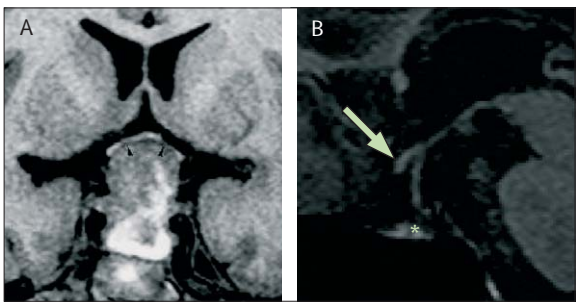

Figure 2: **MRI of patients with different causes of hypopituitarism**
(A) 44-year-old man with total pituitary hormone deficit. Contrast-enhanced, coronal, T1-weighted MRI shows macroadenoma of the pituitary gland with compression of the optic chiasm (arrowheads). (B) 55-year-old man with deficiencies of luteinising hormone and follicle-stimulating hormone and growth hormone after severe traumatic brain injury. Native, sagittal, T1-weighted MRI shows reduced pituitary volume and absence of hyperintense neurohypophyseal signal (asterisk). The arrow shows optic chiasm.

Diagnostic tests

In principle, a combination of low peripheral and inappropriately low (below the upper level of the reference range) pituitary hormones indicates hypopituitarism. However, basal concentrations alone might be not distinctive owing to pulsatile, circadian, or situational secretion of some hormones. Table 4 provides a summary of endocrine testing for pituitary function.

ACTH deficiency

ACTH and cortisol secretion follow a diurnal rhythm, with highest amounts in the early morning and lowest concentrations around midnight. These chemicals are stress hormones. Thus, values in the normal range might still indicate that the ability to respond adequately to stress is impaired. Secondary adrenal insufficiency can be excluded at morning cortisol concentrations greater than 500 nmol/L and is indicated at less than 100 nmol/L.[44] Amounts between these values need a stimulation test. Hypoglycaemia (blood glucose <2·2 mmol/L) induced by the insulin tolerance test (0·1–0·2 IU insulin per kg bodyweight given intravenously as a bolus) is a strong stressor and regarded as gold standard for assessment of the entire hypothalamic-pituitary-adrenal axis. A maximum cortisol response to a peak concentration greater than 500 nmol/L generally excludes adrenal insufficiency. This test has some unpleasant side-effects, such as sweating, trembling, fatigue, and hunger, and is contraindicated in patients with heart disease or epileptic seizures. It should be undertaken only under close supervision at skilled centres. Corticotropin-releasing hormone (100 µg as a bolus) given as a stimulant for the pituitary ACTH reserve is no more predictive of adrenal function than morning cortisol concentrations.[48]

Therefore, it is of limited value for diagnosis of ACTH deficiency.

ACTH deficiency causes adrenal atrophy and ACTH-receptor downregulation.[44] Thus, the standard 250 µg 1-24 ACTH (corticotropin) test can be used to establish secondary adrenal insufficiency if done at least 4 weeks after onset of ACTH deficiency.[49] Stimulated cortisol concentrations at 30 min of 500 nmol/L or less strongly indicate ACTH deficiency, and amounts of more than 600 nmol/L rule out the disorder.[50] At values in between, a second test is recommended. Whether a low-dose (1 µg) corticotropin test would represent a more physiological stimulus for maximum adrenal stimulation than the 250 µg corticotropin dose is debatable. Even though findings of some reports have suggested superior sensitivity for a 1 µg test, workers on a meta-analysis reported comparable operating characteristics of both tests for diagnosis of secondary adrenal insufficiency.[51] The low-dose test has disadvantages, including a need for dilution of the commercially available 250 µg corticotropin dose and repetitive blood sampling. These factors make the standard test more practical. In 20 studies included in the above meta-analysis, overall sensitivity of the 250 µg corticotropin test for diagnosis of secondary hypoadrenalism—with the insulin tolerance test as the gold standard at equal sensitivity and specificity—was 83·5% (95% CI 79·6–87·4). At a specificity of 95%, however, sensitivity was only 57% (44–71). Therefore, the ability of this test to detect all relevant cases of secondary hypoadrenalism has been questioned.[51] However, in a retrospective follow-up of 148 patients with a low-normal cortisol response (510–635 nmol/L) to the 250 µg corticotropin test over a median time of 4·2 years, only two patients developed clear-cut adrenal insufficiency, another two presented with persistent diagnostic uncertainty, and seven had adrenal insufficiency after subsequent pituitary surgery or irradiation.[52] Thus, the 250 µg corticotropin test seems to exclude clinically significant hypoadrenalism, even though—for a definite conclusion—a prospective comparison with the insulin tolerance test would be desirable.

We should bear in mind that no test—including the insulin tolerance test—classifies all patients correctly.[44] Thus, in borderline cases, clinical judgment and follow-up are crucial for assessment of ACTH deficiency.

TSH deficiency

Central hypothyroidism is diagnosed when concentrations of free thyroxine are decreased and TSH amounts are low or normal.[53] Dynamic testing is generally not necessary because it does not add to diagnostic reliability.[54–56] In some cases, TSH can be even slightly raised, owing to secretion of biologically inactive TSH. Tri-iodothyronine is still at normal concentrations in most patients.[53]

	Criteria for hormone deficiency*
Corticotropic function	
Morning cortisol	<100 nmol/L: hypocortisolism; >500 nmol/L: hypocortisolism excluded
Morning ACTH	Below upper reference range: secondary adrenal insufficiency
Insulin tolerance test	Cortisol <500 nmol/L
250 µg ACTH test	Cortisol <500 nmol/L after 30 min
Thyrotropic function	
Free thyroxine	Low (<11 pmol/L)
TSH	Low or normal (occasionally slightly raised)
Gonadotropic function	
Women	
Clinical	Oligoamenorrhoea, oestradiol <100 pmol/L, LH and FSH inappropriately low
Postmenopausal	LH and FSH inappropriately low
Men	
Testosterone	Low (<10–12 nmol/L), LH and FSH inappropriately low
Somatotropic function	
IGF-I	Below or in the normal reference range
Insulin tolerance test	Adults: growth hormone ≤3 µg/L; Children: growth hormone ≤10 µg/L; Transition phase: growth hormone ≤5 µg/L
GHRH+arginine test	Underweight or normal weight (BMI <25): 11·5 µg/L; Overweight (BMI ≥25 to <30): 8·0 µg/L; Obese (BMI ≥30): 4·2 µg/L
GHRH+GHRP-6 test	Growth hormone ≤10 µg/L
Posterior pituitary function	
Basal urine and plasma sample	Urine volume (≥40 ml/kg bodyweight per day)+urine osmolality <300 mOsm/kg water+hypernatraemia
Water deprivation test	Urine osmolality <700 mOsm/kg; Ratio of urine to plasma osmolality <2

LH=luteinising hormone. FSH=follicle-stimulating hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone. GHRH=growth hormone-releasing hormone. GHRP-6=growth hormone-releasing peptide 6. *Hormone levels might differ to the ones indicated, dependent on the laboratory and assay used.

Table 4: **Endocrine testing for pituitary function**

Luteinising hormone and follicle-stimulating hormone deficiency

Before diagnosis of luteinising hormone (LH) and follicle-stimulating hormone (FSH) deficiency, prolactin excess should be excluded, which might be present because of disturbed hypothalamic inhibition of prolactin release. Diagnosis of female LH and FSH deficiency should be based on clinical findings, supported by laboratory values. Oligoamenorrhoea along with inappropriately low LH and FSH concentrations indicates secondary hypogonadism in premenopausal women. During or after menopause, an absence of the typical rise in LH and FSH during menopause shows central hypogonadism. In men, secondary hypogonadism is shown by low testosterone concentrations in combination with inappropriately low gonadotropins. Hypogonadism in childhood causes no clinical symptoms until onset of puberty, at which time it usually presents with delayed or missing onset of puberty.

	Treatment	Monitoring and dose adjustment
ACTH[82,83]	10–25 mg hydrocortisone per day (2–3 doses per day) or 25–37·5 mg cortisone acetate Stress (surgery, infection, etc): increase dose up to 100–150 mg/day[84]	Use the least dose necessary to relieve clinical symptoms; Increase dose during pregnancy[85] Growth hormone replacement might unmask ACTH deficiency and require dose adjustment[86]
TSH	L-thyroxine mean dose after initial uptitration:[53] >60 years: 1·1 µg/kg bodyweight; <60 years: 1·3 µg/kg bodyweight	Adjust to free thyroxine (target: middle-upper normal range) and normal tri-iodothyronine Further adjustments to cholesterol and clinical symptoms; Increase might be necessary during pregnancy or new oestrogen or growth hormone replacement[87-90]
LH/FSH		
Women[85,91,92]	Oral contraceptive (20–35 µg ethinyl oestradiol) or oestradiol valerate 2–4 mg/day or equine oestrogens 0·626–1·250 mg/day or transdermal oestradiol patch or gel (four times less risk of thrombosis); Unless hysterectomised: additional gestagen replacement necessary Induction of fertility: FSH or pulsatile gonadotropin-releasing hormone (the latter only hypothalamic dysfunction)[93]	Use the least dose necessary to relieve clinical symptoms Stop replacement at the age of menopause if possible
Men	Testosterone gel 25–50 mg/day[94,95] or testosterone undecanoate 1000 mg intramuscularly all 12 weeks[96] or buccal testosterone pellet 30 mg twice a day[97,98] or testosterone enanthate 250 mg intramuscularly all 2–4 weeks (causes fluctuating testosterone concentrations); Induction of fertility: human chorionic gonadotropin, human menopausal gonadotropin FSH or pulsatile gonadotropin-releasing hormone (the latter only in hypothalamic dysfunction)[99-104]	Adjust dose to normal testosterone concentrations Monitor for prostate size, prostate-specific antigen, and haematocrit Contraindications for testosterone: prostate cancer, polyglobulia
Growth hormone	Growth hormone dose after up-titration; Children: 25–50 µg/kg per day; Adults: 0·2–1 mg/day	Adjust to normal IGF-I concentrations; Further adjustments to beneficial and unwanted effects (oedema, arthralgias, carpal tunnel syndrome)
ADH	Desmopressin oral (0·3–1·2 mg/day) or intranasal (10–40 µg/day) in 1–4 doses per day[47,105]	Adjust dose to normalisation of fluid intake

LH=luteinising hormone. FSH=follicle-stimulating hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone. ADH=antidiuretic hormone.

Table 5: **Hormone-replacement regimens**

Growth hormone deficiency

In general, growth hormone deficiency needs to be diagnosed by stimulation testing, unless all other pituitary axes are defective and insulin-like growth factor 1 (IGF-I) is low. In these patients, the a-priori-likelihood of the deficiency is 99%.[57] Reference ranges for the growth hormone-regulated chemical IGF-I are helpful for monitoring of growth hormone substitution. However, both IGF-I concentrations and spontaneous growth hormone secretion substantially overlap between patients with both deficient and sufficient amounts of growth hormone, limiting their value for diagnosis of deficiency.

For identification of growth hormone deficiency, the insulin tolerance test is the best choice. Peak amounts of growth hormone of 3 µg/L or lower during the test suggest severe deficiency in adults.[58,59] In children, the secretory capacity of growth hormone is higher and, generally, an arbitrary cutoff of 10 µg/L is used.[60] For patients in the transition phase between puberty and early adulthood, cutoff amounts of 6·1 µg/L[61] or 5 µg/L[62] have been suggested.

The growth hormone-releasing hormone (GHRH) plus arginine test (1 µg/kg of GHRH intravenously as a bolus plus 30 g arginine as an infusion over 30 min) is easy to do, well tolerated, and has been shown to reliably detect severe growth hormone deficiency in a lean adult population when a cutoff of 9 µg/L is used.[63,64] Further work has shown, however, that the growth hormone response to this test declines greatly with increasing body-mass index (BMI),[65,66] and use of this cutoff in obese patients causes a high proportion of false-positive results.[67] Findings of a study in which six different dynamic tests of growth hormone secretion were assessed in an obese study population (mean BMI 31) suggested a cutoff of 4·1 µg/L for the GHRH plus arginine test.[68] In the past few years, BMI-dependent cutoff amounts have become available. The values suggested for lean (BMI <25), overweight (BMI ≥25 to <30), and obese (BMI ≥30) patients are 11·5, 8·0, and 4·2 µg/L, respectively.[69]

Another alternative is the GHRH plus growth hormone-releasing peptide 6 test.[70] This test has been shown to distinguish well between growth hormone-deficient and healthy individuals, although it seems to be of limited sensitivity for hypothalamic disease.[71] A cutoff of 15 µg/L showed the best balance of sensitivity and specificity, and specificity was 100% at a cutoff of 10 µg/L. The glucagon test (1 mg glucagon intramuscularly, growth hormone measurements every 30 min until 240 min after administration) has been shown to separate growth hormone-deficient and healthy patients with a sensitivity and specificity of 100% at a peak amount of 3 µg/L.[72] However, it is dependent on age and BMI[72] and is more time-consuming than other stimulation tests.

We should bear in mind that no test for assessment of growth hormone deficiency is 100% reliable. The likelihood of this chemical deficiency rises with increasing numbers of additional defects in pituitary axes. Normal concentrations of IGF-I in the blood do not exclude a diagnosis of growth hormone deficiency, but such a diagnosis can probably be excluded if low amounts of

this hormone are measured. These aspects, along with clinical signs of growth hormone deficiency and safety considerations, should be taken into account for the decision to start growth hormone substitution.

ADH deficiency

ADH deficiency causes polyuria and polydipsia. Before testing, diabetes mellitus as a typical cause of polyuria should be excluded. Diabetes insipidus is possible if polyuria (≥40 ml/kg bodyweight per day) in combination with urine osmolality less than 300 mOsm/kg water and hypernatraemia is present. If normal amounts of sodium are present in plasma, a water deprivation test will be necessary. This test should be done at a skilled centre and signs of exsiccosis should be monitored closely. Generally, diabetes insipidus can be diagnosed if no clear increase is seen in urine osmolality (maximum <700 mOsm/kg)[47] or the ratio of peak urine to plasma osmolality is less than 2.[73] Glucocorticoids can suppress ADH secretion and, thus, diabetes insipidus might be precipitated by glucocorticoid replacement.[74]

Management

Screening for hypopituitarism

Endocrine assessment of pituitary function is usually prompted by presence of ophthalmological, neurological, or other symptoms, leading to suspicion of pituitary disease. In some disorders, however, pituitary dysfunction should be actively searched for. After pituitary surgery, glucocorticoid replacement should be given to avoid undetected hypoadrenalism until deficits of ACTH and other pituitary hormones are excluded about 4 weeks after surgery.[44] In patients with traumatic brain injury or subarachnoid haemorrhage, a high risk exists for hypopituitarism, but symptoms are usually masked by the sequelae of brain injury. In these individuals, endocrine assessment should be done routinely, particularly in severe or moderate cases[31,75] or if the brain injury has led to prolonged admission.[28]

Treatments of cause

If caused by a tumour, pituitary function might be restored after successful surgical or medical removal of the lesion. The ability to restore pituitary function depends on accessibility, aggressiveness, and size of the tumour, skill of the surgical team, and the chosen operative pathway. In a study of 721 patients undergoing surgery for non-functioning pituitary adenomas, pituitary function improved in 50% and 11% after transsphenoidal and transcranial surgery, respectively, and worsened in 2% and 15%, respectively.[76] In another study of 155 individuals with non-functioning adenomas, however, no substantial improvement of pituitary function was recorded.[77] Craniopharyngiomas that grow aggressively and are difficult to access lead to worse results: previous normal anterior pituitary function is maintained in about 50% and worsens in the remainder.[78,79] Medical treatment of prolactinomas with dopamine agonists restores pituitary function in 60–75%.[80,81]

Generally, unless contraindicated, surgery is the primary treatment for symptomatic pituitary tumours. Neurosurgery aims to prevent deterioration or manifestation of clinical symptoms such as visual disturbances and neurological signs. Particularly, visual-field impairments are a serious sign and should prompt immediate surgical intervention. Prolactinomas are an exception to the rule. They respond very well to dopamine agonist treatment and should undergo primary medical treatment.

For **further information on Diabetes insipidus** see http://www.diabetesinsipidus.org

Hormone substitution

We should remember that hypopituitarism is sometimes accompanied by events such as diabetes mellitus, dyslipidaemia, cardiovascular complications, and osteoporosis. In addition to pituitary hormone substitution, we must treat these disorders adequately with treatments including lifestyle adaptations, lipid-lowering and antihypertensive drugs, or bisphosphonates. Table 5 gives an overview of hormone-substitution regimens.[82–105] Because glucocorticoid deficiency can be life threatening, substitution should begin as soon as a deficit is confirmed. All patients should be supplied with an emergency card or bracelet with information about their steroid dependence and instructions on stress-related dose adjustments. Thyroid hormone substitution with L-thyroxine is necessary if hypothyroidism is identified. Because thyroid hormone replacement increases the rate of metabolism of glucocorticoids, which can lead to an adrenal crisis, replacement therapy should begin after hydrocortisone substitution has been initiated.[53] Female sex hormone substitution can return libido, well being, and bone mass to normal levels. Findings of large studies of sex hormone replacement in non-hypopituitary postmenopausal patients have shown an increased risk of cardiovascular and neoplastic diseases.[106,107] Thus, stopping sex hormone substitution in hypogonadal women after menopause is recommended.

In hypogonadal men, testosterone substitution returned bone and muscle mass, sexual function, and haematocrit to normal levels.[108] Growth hormone substitution enhances body composition, lipid variables, and quality of life.[109] Growth hormone deficiency has been assumed to contribute to the excess cardiovascular mortality seen in hypopituitarism, even though other factors such as cranial radiation, surgery, and other chemical deficits might also have an important role.[109] In some studies, researchers have recorded an improvement of cognitive function,[110,111] although others have noted no effect.[112,113] Findings of long-term studies have shown no increased overall risk of malignant disease or tumour regrowth.[109] However, the recorded numbers of patients are still too small for a final conclusion, and surveys on tumour growth are ongoing.

Follow-up

Once hypopituitarism has been diagnosed, adequate hormone replacement should be monitored at regular intervals. After the initial titrating phase, intervals of 6–12 months are usually recommended. If a tumour is the cause, regular ophthalmological controls and MRI should be undertaken. Endocrine assessment after brain injury should be done initially in the rehabilitation phase (3–6 months after trauma).[31,75] Since pituitary dysfunction can recover after this phase, but sometimes new deficiencies might become manifest, assessment should be repeated in the chronic phase (about 1 year after trauma).[31,75]

Adequate replacement of pituitary hormones can greatly enhance quality of life, morbidity, and mortality associated with hypopituitarism. Research has shown that many groups of patients previously not considered for endocrine assessment are at high risk for hypopituitarism. In these individuals, the disorder should be actively searched for. Current research has not only refined the diagnosis of hypopituitarism but also emphasised the importance of clinical judgment. Many questions about need for and best dose of hormone replacement and clinical follow-up, particularly in patients with post-traumatic hypopituitarism, are still unanswered and need further research.

Conflict of interest statement

HJS has received speaker fees and travel grants from Pfizer and travel grants from Lilly, Novo Nordisk, and Serono. GA has received speaker fees from Pfizer, Novo-Nordisk, and Serono. IK-A has received speaker fees, travel grants, and research grants from Pfizer and Novo Nordisk and travel grants from Ipsen, and is a member of the German KIMS board. GKS has received speaker fees from Pfizer, Novartis, Novo Nordisk, and Serono, travel grants from Pfizer, and research grants from Pfizer, Novartis, and Ipsen. EG has received speaker fees from Pfizer, Serono, Eli-Lilly, Novartis, and Ipsen.

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