REVIEW

Aetiology, diagnosis, and management of hypopituitarism in adult life

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Hypopituitarism is a complex medical condition associated with increased morbidity and mortality, requires complicated treatment regimens, and necessitates lifelong follow up by the endocrinologist. The causes, clinical features, and the management of hypopituitarism including endocrine replacement therapy are considered in this review article.

Hypopituitarism is defined as either partial or complete deficiency of anterior or posterior pituitary hormone secretion, or both. Regal *et al*[1] reported a prevalence of 45/100 000 and an incidence of about 4/100 000/year in the normal population, with nearly 50% of patients having three to five pituitary hormone deficits. It is a complex medical condition associated with a higher mortality than that of the general population.[2–5]

AETIOLOGY

Of the various causes of hypopituitarism in adults (see box), pituitary adenoma or its treatment by surgery and/or radiotherapy is by far the commonest. Macroadenomas (greater than 1 cm) are associated with one or more trophic hormone deficits in 30% of cases[6]; direct compression and destruction of the surrounding normal pituitary leads to hyposecretion. Other postulated mechanisms include primary mass effect of the tumour on the vascular portal system/pituitary stalk, raised intrasellar pressure affecting portal circulation, and focal pituitary necrosis secondary to prolonged interruption of portal blood supply.[7 8] While microadenomas (less than 1 cm) rarely affect pituitary function,[8] prolactin producing microadenomas often present with hypogonadism because of the suppressive action of a high prolactin (PRL) level on gonadotrophins' (follicle stimulating hormone FSH and luteinising hormone LH) secretion. Among the peripituitary tumours causing central endocrine dysfunction, craniopharyngioma is the commonest.

Occurrence of hypopituitarism after pituitary surgery is influenced by tumour size, extent of invasion into surrounding structures, remaining viable normal pituitary, and the skill of the neurosurgeon. Transient postoperative diabetes insipidus (DI) is seen in 5% of cases but permanent DI occurs less frequently. At least partial recovery of pituitary function in 40%–65% of patients has been reported after surgery[7 9–11] but postoperative deterioration has also been reported.[12] Patients should be made aware of the possibility of hypopituitarism before surgery. Post-surgical endocrine assessment is mandatory.

Anterior hypopituitarism may follow cranial radiotherapy used in treating various intracranial tumours, acute lymphoblastic leukaemia (prophylactic cranial radiotherapy), and those receiving total body irradiation. The impact is dependent on the total dose, fractionation, duration of treatment, and time elapsed since radiation exposure to the hypothalamic-pituitary axis.[13 14] In one series after a radiotherapy dose to the hypothalamic-pituitary axis of 37.5 to 42.5 Gy, after five years all patients were growth hormone (GH) deficient, 90% gonadotrophin deficient, 77% adrenocorticotrophic hormone (ACTH) deficient, and 42% were thyroid stimulating hormone (TSH) deficient.[13] Gamma knife surgery for pituitary adenoma has recently been reported to affect pituitary function less than conventional radiotherapy[15] although these are preliminary findings and require long term studies to determine if this is the case. Congenital isolated/multiple pituitary hormone deficiencies (MPHD) have been described. Growth hormone gene GH-1[16] and growth hormone releasing hormone receptor gene GHRH-R[17] mutations can result in isolated growth hormone deficiency where as KAL gene defect is implicated in the X-linked form of Kallman's syndrome (isolated hypogonadotrophic hypogonadism plus hypo/anosmia). Table 1 lists the genetic forms of MPHD.

Lymphocytic hypophysitis first described in 1967[18] is recognised as an autoimmune disorder mainly of the adenohypophysis[19] wherein isolated/combined ACTH/TSH/gonadotrophin/GH deficiencies and rarely, DI[20] have been reported. It is an uncommon condition predominantly affecting women in late pregnancy or the early

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Abbreviations: NFPA, non-functioning pituitary adenoma; PRL, prolactin; FSH, follicle stimulating hormone; LH, luteinising hormone; DI, diabetes insipidus; GH, growth hormone; ACTH, adrenocorticotrophic hormone; TSH, thyroid stimulating hormone; MPHD, multiple pituitary hormone deficiencies; MR, magnetic resonance; CSF, cerebrospinal fluid; BMD, bone mineral density; IGF1, insulin-like growth factor 1; GHD, growth hormone deficiency; AGHD, adult growth hormone deficiency; ITT, insulin tolerance test; GHRH, growth hormone releasing hormone; GST, glucagon stimulation test; HPA, hypothalamic-pituitary-adrenal; TRH, thyrotrophin releasing hormone; GnRH, gonadotrophin releasing hormone; HCG, human chorionic gonadotrophin; SMR, standardised mortality ratio; HRT, hormone replacement therapy; QoL, quality of life; HC, hydrocortisone; PSA, prostate specific antigen

postpartum period[21] who present with headache and visual field defects. Magnetic resonance (MR) scan is suggestive of the diagnosis but histology is the gold standard. In subclinical disease, spontaneous remission is reported but in patients with hypocortisolism or symptomatic extrasellar expansion, medical treatment and/or neurosurgical decompression is recommended.[22]

Hypopituitarism after head injury tends to occur mostly within one year of injury,[23] and Aimaretti *et al*[24] reported some degree of deficiency in 35% of cases at three months after brain injury (trauma/subarachnoid haemorrhage), not specifically related to the level of consciousness (Glasgow coma scale). Growth hormone and gonadotrophin deficiencies are most common,[23 25] and mandatory neuroendocrine assessment has been recommended, given the potential therapeutic implications.

Pituitary apoplexy refers to abrupt destruction of pituitary tissue after infarction/ haemorrhage within the tumourous/ non-tumourous pituitary gland, clinically characterised by acute onset headache, vomiting, visual impairment, and meningism. Partial or complete, transient or permanent hypopituitarism may result.[26] MR scan is diagnostic; if visual deficits are present, trans-sphenoidal surgery may be considered and that has been reported to be safe and effective.[27] Postpartum pituitary necrosis is referred to as Sheehan's syndrome.

Table 1 Genetic forms of isolated and multiple pituitary hormone deficiencies

Defective/mutant gene	Disease
GH-1 GHRH-R	Isolated growth hormone deficiency
TPit	Isolated ACTH deficiency
GnRH-R	Isolated hypogonadotrophic hypogonadism
KAL	X-linked Kallman's syndrome
PIT 1	GH, PRL, TSH deficiency
PROP 1	GH, PRL, TSH, FSH/LH ± partial ACTH deficiency
HESX1/Rpx	Septo-optic dysplasia with isolated growth hormone deficiency/ panhypopitutarism
LHX3/4	MPHD + cranial structural abnormalities
DAX-1	X-linked AHC (adrenal hypoplasia congenita) + hypogonadotropic hypogonadism

Causes of hypopituitarism

Congenital
- Isolated / multiple pituitary hormone deficits (MPHD)

Pituitary and peripituitary tumours
- Non-functioning pituitary adenoma (NFPA)
- Functioning pituitary adenomas
  - Prolactinoma
  - Growth hormone secreting
  - ACTH secreting
  - TSH secreting
  - Gonadotrophin secreting
- Posterior pituitary tumours
  - Ganglioneuroma, astrocytoma
- Peripituitary lesions
  - Craniopharyngioma
  - Meningioma
  - Chordoma
  - Optic nerve glioma
  - Germinomas
- Metastatic
  - Breast, lungs, colon, prostate

Pituitary surgery
Cranial radiotherapy
Infiltrative conditions
- Sarcoid, histiocytosis X, lymphocytic hypophysitis, primary haemochromatosis

Infections
- TB, syphilis, mycoses

Head injury
Vascular
- Pituitary apoplexy
- Carotid artery aneurysm
- Subarachnoid haemorrhage

CLINICAL FEATURES

The underlying pathology, severity, and the speed of onset of hypopituitarism influences the clinical picture.

Space occupying lesions causing hypopituitarism may result in symptoms such as headache, visual disturbances and rarely, personality changes, temporal lobe epilepsy, and cerebrospinal fluid (CSF) rhinorrhoea. In addition to symptoms and signs attributable to pressure effects on the pituitary gland including the stalk, actively secreting tumours can consequently produce a complex picture of combined hormonal excess and deficiencies, for example, GH secreting macroadenoma causing acromegaly and hypogonadism. Mild ACTH deficiency may be unmasked during an intercurrent illness, while severe hypopituitarism after pituitary apoplexy presents as a medical emergency. The presence of DI usually suggests a hypothalamic or stalk disorder, except when it follows intracranial surgery. Table 2 lists the clinical features of the individual hormone deficiencies.

DIAGNOSIS

The diagnosis entails clinical examination, biochemical assessment, and investigation of the cause of hypopituitarism.

A thorough physical examination including visual fields' assessment is essential. Goldmann perimetry helps in plotting the visual field defects and assists in follow up.

Simultaneous measurements of basal anterior pituitary and target organ hormone levels provide useful information to help establish the cause. TSH, thyroxine, FSH, LH, oestradiol (women)/testosterone (men), prolactin, insulin-like growth factor 1 (IGF1) and 9 am cortisol form the baseline tests. Dynamic/provocative tests are necessary to assess GH secretory reserve[28] and the ACTH-adrenal axis comprehensively.

Growth hormone deficiency (GHD)

Adult growth hormone deficiency (AGHD) should only be considered within an appropriate clinical context (patients with primary hypothalamic-pituitary disease or those exposed to traumatic brain injury, subjects who had received cranial irradiation previously, or those with childhood onset GHD), and defined biochemically.[28 29] In an obese patient, the

Table 2 Symptoms and signs of pituitary insufficiency

Hormone deficiency	Clinical features
Growth hormone	Reduced energy and vitality Reduced muscle mass and strength Increased central adiposity Decreased sweating and impaired thermogenesis Increased cardiovascular risk Reduced bone mineral density (BMD)
Adrenocorticotrophic hormone	Fatigue, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, hypoglycaemia, circulatory collapse if acute onset; loss of axillary and pubic hair in women
Gonadotrophins	Men: erectile dysfunction, soft testes, reduced muscle mass, erythropoiesis, reduced energy and vitality Women: oligomenorrhoea/amenorrhoea, dyspareunia, breast atrophy Both: loss of libido, flushes, infertility, regression of sexual characteristics, reduced BMD.
Thyroid stimulating hormone	Fatigue, apathy, cold intolerance, constipation, weight gain, dry skin, psychomotor retardation.
Antidiuretic hormone	Polyuria, polydipsia, nocturia.
Prolactin	Inability to breast feed

diagnosis of isolated severe GHD can be difficult to substantiate because of the influence of visceral fat mass on GH status; diagnostic difficulties may also occur in certain pathophysiological disorders such as ''cured'' acromegaly attributable to the persistence of qualitative abnormalities in GH secretion.[30] Under the latter circumstances heavy reliance is placed on the presence of a abnormally low IGF1 concentration.

The consensus is that adult patients with hypothalamic-pituitary disease and one or more additional pituitary hormone deficits require only one GH provocative test while those with suspected isolated GHD need two GH stimulatory tests.[29] About 40%–60% of those with a putative diagnosis of childhood onset GHD may have an impaired GH response in adult life.[31]

An insulin tolerance test (ITT) is regarded as the ''gold standard'' test in adults and severe deficiency is said to exist when the peak GH response is less than 3 μg/l (9 mU/l). After an overnight fast, intravenous insulin 0.05–0.15 units/kg is injected and samples are taken for blood glucose and GH levels at 0, 30, 60, 90, 120 minutes. Definition of a normal GH response to an ITT performed with an appropriate degree of hypoglycaemia (blood glucose <2.2 mmol/l) is a peak of at least 5 μg/l.[32] Performed with adequate supervision in specialised units, an ITT is a safe procedure.[33] The ITT also permits concomitant assessment of ACTH status. Despite the debate about its reproducibility,[34] the ITT remains the best validated test. Contraindications to an ITT include ischaemic heart disease, an abnormal resting ECG, arrhythmias, epilepsy/ unexplained blackouts, etc.

Other stimulatory tests used either as a second test for the diagnosis of GHD or if the ITT is contraindicated, are necessary. The combined growth hormone releasing hormone (GHRH) + arginine test presents an excellent alternative with defined thresholds.[35] The use of the GH secretogoge, hexarelin[36] combined with GHRH in young and middle aged adults[37] with age specific cut offs is one of the more recently introduced tests.

Other widely used tests include glucagon stimulation (GST) and arginine stimulation. Glucagon is more potent than arginine in assessing GH reserve,[38] and provides a reliable alternative.[39] GST allows for simultaneous testing of both GH and ACTH reserve.

Circulating IGF1 can be helpful in the diagnosis of adult GHD, however, there are alternative causes of a low IGF1 level other than GHD; these include malnutrition, liver disease, diabetes mellitus, and hypothyroidism. Sufficient age adjusted normative data are crucial for interpretation of patient's IGF1 concentrations. The IGF1 estimation is most helpful in the young adult with severe GHD, and with increasing age the IGF1 concentration is less likely to be abnormally low in GHD patients[40] such that only 17% of severely growth hormone deficient adults over the age of 65 years have an IGF1 concentration below the normal range.

ACTH deficiency

A basal (9 am) cortisol less than 100 nmol/l[32 41] in untreated patients, or greater than 450–500 nmol/l[33 42] obviates the need for provocative tests of ACTH reserve without compromising patient care. If cortisol insufficiency is clinically suspected, particularly in an unwell patient, basal cortisol and ACTH samples are taken but cortisol replacement started awaiting results. The ITT remains the gold standard for assessing the entire hypothalamic-pituitary-adrenal (HPA) status and has been cross validated historically against a physical stress (major surgery), with a normal peak cortisol response of 580 nmol/l.[43] In response to hypoglycaemia (less than 2.2 mmol/l), a cortisol level greater than 500 nmol/l is considered to be consistent with normal ACTH status. An ITT however is not without contraindications or morbidities and hence several authors advocate the short synacthen test (SST) with appropriate cut offs as the first line test.[44 45] While controversy exists about the cut offs and diagnostic reliability,[46 47] the potential for missing subtle HPA defects remains a possibility; a 30 minute cortisol (after intramuscular synacthen 250 μg) of greater than 550 nmol is considered to represent a ''pass''. An ITT should be performed in those who fail the screening SST.

Other tests include the GST, to which the peak cortisol response is less than that to the ITT and occurs later.[48]

Patients with borderline cortisol responses to ITT (450–500 nmol/l) may only require glucocorticoid replacement during intercurrent illness/surgery.

TSH deficiency

TSH deficiency is indicated by low basal serum free/total thyroxine with an inappropriately normal or low TSH. Routine use of a thyrotrophin releasing hormone (TRH) stimulation test is not advocated[41] in adults.

Gonadotrophin deficiency

This is associated with low serum testosterone in the presence of normal or low gonadotrophin levels in men and low serum oestradiol concentrations in pre-menopausal women without appropriately increased gonadotrophins, and in post-menopausal women the absence of the normal rise of gonadotrophin concentrations. The use of a gonadotrophin releasing hormone (GnRH) provocation test does not provide any additional information in adults.[41]

Antidiuretic hormone (ADH) deficiency

Under normal circumstances ADH release from the posterior pituitary is mainly influenced by changes in plasma osmolality. In cranial DI, lack of such a response results in large urinary volumes (greater than 3 l/day or 40 ml/kg/day) of low osmolality (less than 300 mOsmol/kg); ACTH deficiency can mask DI clinically, symptoms only becoming apparent on starting steroid replacement.

The standard eight hour water deprivation test entails closely supervised dehydration of a previously well hydrated patient, during which basal and hourly plasma and urine osmolalities, and urine volumes are measured as well as weight estimated two hourly (if >3% weight loss occurs, the

test is terminated). After eight hours, intramuscular desmopressin 2 μg is injected, and blood and urine osmolalities and urine volumes are remeasured. Urine, dilute (less than 300 mOsmol/kg) at the end of fluid deprivation becomes concentrated (greater than 750 mOsmol/kg) after desmopressin in patients with cranial DI, but remains dilute in nephrogenic DI. In borderline cases (urine osmolality 300–750 mOsmol/kg pre-desmopressin and less than 750 mOsmol/kg after the injection), a more definitive assessment with the hypertonic saline infusion test will aid the diagnosis.[49]

INVESTIGATIONS

Radiological assessment

The presence of clinical and biochemical evidence of hypopituitarism necessitates imaging studies of the hypothalamic-pituitary region, and MR imaging is currently the investigation of choice.[6] When it is not possible, CT scan with contrast provides a suitable alternative. In cranial DI, the normal high intensity posterior-pituitary bright spot on T1 weighted MR is generally absent.[50] It is worth noting, however, that in necropsy studies of people with no known hypothalamic-pituitary disorder, pituitary microadenomas may be found in 10%–20%.

Other investigations

Serum and CSF angiotensin converting enzyme activities (neurosarcoid), serum ferritin (haemochromatosis), human chorionic gonadotrophin (HCG) (germ cell tumours), etc, may provide additional information to elicit the aetiology. Genetic testing is particularly helpful in isolated/syndromic MPHD.

IMPLICATIONS OF UNTREATED PITUITARY HORMONE DEFICIENCY

Patients with hypopituitarism have an increased mortality. Our current knowledge is based on six major retrospective studies, most of which confirmed excess mortality in hypopituitary patients.

The first large study in hypopituitary patients came from Sweden in 1990. Rosen *et al*[2] gathered mortality data in 333 hypopituitary patients, and found deaths from vascular disorders twice as common compared with the age and sex matched population; this was independent of the underlying cause for hypopituitarism or the degree of pituitary insufficiency. In their discussion, the authors proposed untreated GHD as the probable underlying cause of the excess mortality.

In 1996, Bates *et al*[3] studied mortality data in 172 patients with hypopituitarism (mainly attributable to pituitary tumours) receiving standard endocrine replacement therapy. Of 98 patients tested for their GH status, 94 had confirmed GHD. Women had a higher standardised mortality ratio (SMR) than men (2.29 *v* 1.5). The only significant independent predictive factors for survival were age at diagnosis and hypogonadism, the latter being associated with a better prognosis than eugonadism. Only 27% of women were receiving HRT, and vascular deaths were (non-significantly) more frequent in women. In the authors' follow up study[51] with twice as many patients, only a slight and non-significant increase in mortality was seen. Even more surprisingly, risk of vascular death was now significantly reduced in women with a SMR as low as 0.5 ($p<0.01$), whereas male mortality was no different from the normal population.

Bulow *et al*[4] studied the causes of 188 deaths in 344 hypopituitary patients after surgery for pituitary tumours. Cerebrovascular deaths were more common (overall SMR 3.4, female SMR 4.9), contributing to the increased overall mortality (SMR 1.4). Younger age at diagnosis and female sex were independent risk factors of increased mortality.

Two studies in this century reviewed mortality data in larger number of hypopituitary patients. Nilsson *et al*[52] reviewed 842 death certificates of patients from the Swedish Cancer Registry that included 3321 patients with pituitary tumours, and found a SMR of 2.0. Cardiovascular and cerebrovascular death rates were higher than in the normal population (SMR 1.6 and 2.4 respectively), and women had an even higher mortality compared with men (SMR 2.3 *v* 1.9). Limitations of the study were the unknown pituitary status of these patients and reliance on death certification.

The most recent British publication was by Tomlinson *et al*[5] who analysed 181 deaths in 1014 hypopituitary patients, with excess mortality ratios seen particularly in women (2.29 *v* 1.57 in men). Cardiovascular, respiratory, and cerebrovascular SMRs were increased between 1.82 and 2.44. Hormone deficiencies and their treatment were not found to be independent risk factors except for untreated gonadotrophin deficiency. Growth hormone status was reported in 111 patients (11%), and GHD was present in the great majority of these patients (89%). The small total number of 37 patients with normal GH status or treated GHD (13 and 24 patients respectively) prohibits meaningful subanalysis of the role of GHD on mortality, and it was on those grounds, that the authors' dismissal of a role of GHD towards excess mortality was subsequently criticised.[53–55]

While most of the studies above confirmed the excess mortality in hypopituitary patients, no clear answer has emerged with regards to causal relation. It has proved very difficult to be certain about the individual contribution of each risk factor in the very heterogeneous population of hypopituitary patients. GH sufficient and GH deficient patients with pituitary disease are not comparable for a number of reasons: preserved GH secretion is almost always associated with completely normal pituitary function or a less severe degree of hypopituitarism, and the insult to the hypothalamic-pituitary axis in general would have been less noticeable in most of them. While it is comparatively straightforward to stratify patients according to other hormone deficits, underlying disorder, radiotherapy, etc, GHD largely escapes such subanalyses because of the high prevalence of GHD in hypopituitary patients. This is because of the high susceptibility of the somatotroph axis to damage from various insults, be it a pituitary mass lesion, pituitary surgery, hypothalamic irradiation, etc. With a GHD prevalence of more than 95% in hypopituitary patients, the numbers of non-GHD patients are often simply too small to examine the possibility of GHD as an independent mortality risk factor.

It is also not clearly established how and to what extent other treatments in hypopituitary patients contribute to vascular risk, but all have been incriminated in a worsened risk profile, for example, sex steroid treatment, corticosteroid replacement, and pituitary radiotherapy.

Prolactin deficiency suppresses the ability to lactate but no other consequence is known. Prolactin deficiency however implies severe GHD,[56] as prolactin deficiency unlike GHD occurs late in the evolution of hypopituitarism.

MANAGEMENT OF HYPOPITUITARISM

The treatment of hypopituitarism includes therapies directed at the underlying disease process, and endocrine replacement therapy. The pituitary tumours may be treated with medical therapy, surgery, radiotherapy, or a combination of these modalities. A macroprolactinoma, for instance, is amenable to treatment with dopamine agonists,[57] while there is a high surgical cure rate for GH secreting microadenoma by skilled

Table 3 Pituitary hormone replacement therapy

Hormone deficiency	Replacement	Usual dose
Growth hormone	Growth hormone	0.27–0.7 mg subcutaneously in the evening
ACTH	Hydrocortisone	10 mg on rising, 5 mg at noon, 5 mg early evening
TSH	Thyroxine	75–150 μg/day
Gonadotrophins		
Men	Testosterone esters (for example, Sustanon)	250 mg intramuscularly every 2–3 weeks
	Transdermal testosterone	
	Patch (for example, Andropatch)	2.5–7.5 mg/24 hours
	Gel (for example, Testogel)	5–10 g gel/24 hours
	Testosterone implant	600–800 mg every 4–6 months
	Buccal testosterone (for example, Striant SR)	1 buccal tablet (30 mg) applied to the gum every 12 hours
	Oral testosterone (for example, Restandol)	40–120 mg daily
Women	Conjugated equine oestrogens	0.625–1.25 mg daily orally
	or	
	Estradiol valerate	1–2 mg daily orally
	Transdermal estradiol (patch)	25–100 μg/24 hours
	Oestrogen plus progesterone (cyclical/continuous)	Dose depends on preparation—orally or transdermal
ADH	Desmopressin	300–600 μg daily in 2–3 divided doses orally. 10–40 μg daily in 2–3 divided doses intranasally
Prolactin	nil	

surgeons.[58] A recurrent ACTH producing pituitary neoplasm is likely to require a combination of treatments[59] whereas debulking surgery followed by radiotherapy if there is tumour regrowth is the acceptable approach for NFPA.[60]

Surgical decompression is usually required for pituitary and peripituitary tumours causing pressure effects and not responding to medical therapy. Pituitary endocrine status needs reassessing after treatment as functional improvements have been noted.[7 8]

Hormone replacement therapy (HRT)

The goals of HRT in hypopituitarism are to achieve normal levels of the circulating hormones, to restore normal physiology as closely as possible, and to avoid the symptoms of deficiency with minimal side effects. Target hormone rather than the deficient pituitary hormone is replaced except for GH deficiency, ADH deficiency, and when fertility is desired. Table 3 summarises the regimens of HRT.

Educating the patients about their disease forms an important aspect of the management, including its influence on their daily life and the need to modify/change the treatment during intercurrent illness, surgery, etc.

GH deficiency

With the production of human biosynthetic GH by DNA recombinant techniques in the late 1980s, studies followed culminating in the emergence of treatment guidelines for the AGHD syndrome.

This syndrome is characterised by abnormal body composition (increased fat mass and reduced lean body mass), reduced exercise tolerance and muscle strength, osteopenia, an adverse lipid profile, increased procoagulation factors, impaired cardiac function, and reduced psychological well-being.[61 62] All patients with reported severe AGHD are eligible for GH replacement[29] but currently in the UK, the National Institute for Health and Clinical Excellence[63] recommends GH replacement for those adults with biochemically confirmed severe GHD, already taking full pituitary hormone replacement as appropriate and who have severe impairment of quality of life (QoL-AGHDA questionnaire) assessed objectively. The administration of GH to GHD adults reverses many of the adverse changes in body composition, bone mineral density, exercise capacity and strength, and improves the lipid profile.[62 64 65] In those with severe GHD, GH replacement considerably improves QoL in the majority of cases in whom it is impaired at baseline. It should also be appreciated that therapeutic strategies differ worldwide as far as adult GH replacement is concerned. In certain countries (Scandinavia) a more holistic approach is adopted on the premise that this is simply beneficial hormone replacement for a recognised deficiency; alternatively in other countries adult GH replacement is not licensed (Australia) and therefore cannot be prescribed outside of a trial, while elsewhere there are still some endocrinologists who remain unconvinced about the solidity of the evidence base underpinning GH replacement for adults and therefore do not recommend it.

Previous weight based regimens have been replaced by individualised dosing regimens aiming at normalising age and sex matched IGF1 concentrations. The starting dose of human GH is 0.2–0.3 mg given daily as a subcutaneous injection titrating the dose every four to six weeks gradually on the basis of clinical and biochemical responses (IGF1 SD score).[29] Improvement in body composition and QoL often takes several months,[66] and a trial period of six months is recommended after an initial three month period of dose adjustment. Body composition and QoL is reassessed at that stage; failure to show a significant improvement in the QoL assessed objectively (AGHDA questionnaire) will lead to the withdrawal of therapy.[63]

Side effects (seldom seen using modern day dose replacement schedules) include headache, arthralgia, myalgia, fluid retention, etc, and respond to dose reduction. Monitoring includes regular measurements of weight, BP, IGF1, fasting glucose, HbA1c, lipid profile, waist-hip ratio, and two yearly bone densitometry in those with initial low BMD together with patient interview. Absolute contraindications are active malignancy, benign intracranial hypertension, and proliferative/preproliferative diabetic retinopathy. GH is presently not licensed for use during pregnancy and lactation.

There is no evidence of increased rate of recurrence or regrowth of pituitary/peripituitary tumours in GHD patients on GH replacement, but the standard recommendation is to perform baseline pituitary imaging in all patients with a history of pituitary disorder before starting GH replacement therapy.[67]

ACTH deficiency

In ACTH deficient patients, glucocorticoid replacement is essential for life, and optimisation of replacement is important to avoid the long term consequences of over-treatment such as osteoporosis, central obesity, etc[68] whereas under-treatment is potentially life threatening.[69] Hydrocortisone (HC) simply replaces the missing hormone and hence is the preferred agent[70]; less attractive alternatives include cortisone acetate, prednisolone, and dexamethasone.

Estimated endogenous cortisol production has been shown to be 5.7 mg/m^2/day,[71] and thus previous conventional HC replacement of 30 mg/day in divided doses[72] represented over-treatment.[68] More recent evidence suggests that a more normal cortisol profile and patient response is achieved with a dosing regimen of HC of 10 mg on rising, 5 mg at lunchtime, and 5 mg in the early evening[70] rather than twice daily therapy. A twofold to threefold increase in corticosteroid dose is needed temporarily during an intercurrent illness, surgery etc; therefore educating patients and their carers repeatedly is recommended.[73] A medic alert bracelet/necklace should be worn at all times by the patient.

The efficacy of the replacement is assessed both clinically and biochemically. While a 24 hour urinary free cortisol estimation is felt to be a reliable indicator of pronounced over-replacement with HC,[68] an eight hour serum cortisol day curve, or modified three point curve can help detect subclinical over-replacetment or under-replacement.[70]

TSH deficiency

Thyroxine is the treatment of choice taken once a day, starting with 100 μg in young patients and in the absence of cardiac disease, and 25 μg in elderly patients and those with coronary artery disease.[74] ACTH deficiency should be identified and treated if present before starting thyroxine replacement. In patients with pituitary disease, TSH monitoring is unhelpful and therefore its measurement is pointless; the goals of thyroxine replacement should be clinical improvement along with the placing of the serum free thyroxine level within the normal range.[75] Long term over-treatment may result in an increased risk of atrial fibrillation and reduced BMD.

Gonadotrophin deficiency

In men

Androgen replacement therapy has beneficial effects on body composition, sexual function, mood, behaviour, and BMD.[76 77] The route of delivery depends on availability and patient choice. Deep intramuscular injection of a mixture of testosterone esters every two to three weeks is commonly used but is associated with widely fluctuating testosterone levels. Transdermal patches, transdermal gel, and recently introduced buccal preparation offer alternatives with the attraction of more stable serum testosterone concentrations.

Oral testosterone replacement is of limited use given the unreliable bioavailability, varying serum testosterone level, and multiple dosaging. Subcutaneous implants every four to six months require minor surgery and may be complicated by extrusion, local infection, and scarring.

Symptoms and serum testosterone levels guide adequacy of replacement. Monitoring entails measuring haemoglobin, packed cell volume, lipid profile, and prostate specific antigen (PSA) levels. This treatment is contraindicated in patients with prostate cancer (past and current) and male breast cancer.

In women

Oestrogen replacement alleviates the symptoms of deficiency, and is bone protective[78]; hence oestrogen alone in patients without a uterus or with cyclical/continuous progesterone in patients with an intact uterus is usually prescribed. Most endocrinologists treat these patients up to the age of 50 years and re-evaluate the risks and benefits of further use as in other postmenopausal women. The long term impact of oestrogen replacement on cardiovascular morbidity or development of breast cancer in hypopituitary patients is unknown.[79]

Testosterone replacement in women

Hypothalamic or pituitary abnormalities either structural or functional, are associated with a decrease in gonadotrophin secretion and possible impairment of ACTH secretion, thereby reducing both ovarian and adrenal androgen production. Symptoms such as low libido, persistent unexplained fatigue, and decreased sense of wellbeing have been noted together with negative impact on lean body mass and BMD.[80] Ensuring adequate oestrogen replacement and excluding other causes of the above symptoms, a trial of low dose testosterone replacement could be considered,[80] but a firm evidence base for this practice does not exist.

Fertility in hypogonadotrophic hypogonadism

In men

In secondary hypogonadism, spermatogenesis and fertility can be induced. In hypothalamic disorders, pulsatile GnRH given via a subcutaneous pump or subcutaneous injections of gonadotrophins can be used, while in pituitary insufficiency gonadotrophins only are capable of being effective; however the response depends on the pre-treatment testicular volume and if there is any history of testicular maldescent.[81] Androgen replacement should be stopped at least four weeks before fertility treatment. Traditionally, HCG 1000–2000 IU alone is given subcutaneously/intramuscularly two to three times a week for six months; FSH in the form of highly purified urinary human menopausal gonadotrophin, or recombinant FSH is added if adequate spermatogenesis is not achieved on HCG alone.

In women

Regimens of ovulation induction in hypopituitarism are influenced by the underlying disorder. In gonadotrophin deficiency, treatment regimens should include preparations with LH activity to ensure an adequate oestrogen response.[82] Where a structural lesion of the pituitary is the cause, the GnRH pump is unlikely to be effective.[83] If the pituitary failure is secondary to hypothalamic dysfunction, pulsatile GnRH therapy may be the more attractive physiological option.

ADH deficiency

In mild cranial DI (urine output less than 4 l/day), adequate oral fluid intake should suffice whereas in more severe form, desmopressin is the treatment of choice.[84] It is given as an oral, intranasal, or parenteral preparation to control symptoms. Overdose carries the risk of hyponatraemia, and hence sodium levels should be measured after starting treatment and whenever the dose is changed.

CONCLUSION

Hypopituitarism is associated with increased mortality and morbidity, necessitates complicated treatment regimens, and significantly affects the economy of the healthcare system. Strategies to limit the use of conventional radiotherapy may

well lead to a reduced incidence of hypopitutarism. It is probable that hormonal treatment that approaches normal physiology might have a favourable influence on the adverse outcomes; therefore optimising replacement and lifelong follow up is appropriate.

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REFERENCES

1 **Regal M**, Paramo C, Sierra SM, *et al.* Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)* 2001;**55**:735–40.
2 **Rosen T**, Bengtsson B-A. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990;**336**:285–8.
3 **Bates AS**, Van't Hoff W, Jones PJ, *et al.* The effect of hypopituitarism on life expectancy. *J Clin Endocrinol Metab* 1996;**81**:1169–72.
4 **Bulow B**, Hagmart L, Mikoczy Z, *et al.* Increased cerebrovascular mortality in patients with hypopituitarism. *Clin Endocrinol (Oxf)* 1997;**46**:75–81.
5 **Tomlinson JW**, Holden N, Hills RK, *et al.* Association between premature mortality and hypopituitarism. *Lancet* 2001;**357**:425–31.
6 **Vance ML**. Hypopituitarism. *N Engl J Med* 1994;**330**:1651–62.
7 **Arafah BM**. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. *J Clin Endocrinol Metab* 1986;**62**:1173–9.
8 **Arafah BM**, Prunty D, Ybarra J, *et al.* The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. *J Clin Endocrinol Metab* 2000;**85**:1789–93.
9 **Comtois R**, Beauregard H, Somma M, *et al.* The clinical and endocrine outcome to transsphenoidal microsurgery of non-secreting pituitary adenomas. *Cancer* 1991;**68**:860–6.
10 **Marazuela M**, Astigarraga B, Vicente A, *et al.* Recovery of visual and endocrine function following transsphenoidal surgery of large non-functioning pituitary adenomas. *J Endocrinol Invest* 1994;**17**:703–7.
11 **Webb SM**, Rigla M, Wägner A, *et al.* Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. *J Clin Endocrinol Metab* 1999;**84**:3696–700.
12 **Harris PE**, Afshar F, Coates P, *et al.* The effects of transsphenoidal surgery on endocrine function and visual fields in patients with functionless pituitary tumours. *Q J Med* 1989;**71**:417–27.
13 **Littley MD**, Shalet SM, Beardwell CG, *et al.* Hypopituitarim following external radiotherapy for pituitary tumors in adults. *Q J Med* 1989;**70**:145–60.
14 **Littley MD**, Shalet SM, Beardwell CG, *et al.* Radiation induced hypopituitarism is dose dependent. *Clin Endocrinol (Oxf)* 1989;**31**:363–73.
15 **Feigl GC**, Bonelli CM, Berghold A, *et al.* Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. *J Neurosurg* 2002;**97**:415–21.
16 **Cogan JC**, Phillips JA III, Sakati N, *et al.* Heterogeneous growth hormone (GH) gene mutations in familial GH deficiency. *J Clin Endocrinol Metab* 1993;**76**:1224–8.
17 **Wajnrajch MP**, Gertner JM, Harbison MC, *et al.* Nonsense mutation in the human growth hormone-releasing hormone receptor causes growth failure analogous to the little (lit) mouse. *Nat Genet* 1996;**12**:88–90.
18 **Goudie RB**, Pinkerton PH. Anterior hypophysitis and Hashimoto's disease in a young woman. *J Pathol Bacteriol (Lond)* 1962;**83**:584–5.
19 **Thodou L**, Asa SL, Kontogeorgos G, *et al.* Lymphocytic hypophysitis: clinicopathological findings. *J Clin Endocrinol Metab* 1995;**80**:2302–11.
20 **Hashimoto K**, Takao T, Makino S. Lymphocytic adenohypophysitis and lymphocytic infundibuloneurohypophysitis. *Endocr J* 1997;**44**:1–10.
21 **Beressi N**, Beressi JP, Cohen R, *et al.* Lymphocytic hypophysitis—a review of 145 cases. *Ann Intern Med* 1999;**150**:327–41.
22 **Bellastella A**, Bizzarro A, Coronella C, *et al.* Lymphocytic hypophysitis: a rare or underestimated disease? *Eur J Endocrinol* 2003;**149**:363–76.
23 **Benvenga S**, Campenni A, Ruggeri RM, *et al.* Clinical review 113: hypopituitarism secondary to head trauma. *J Clin Endocrinol Metab* 2000;**85**:1353–61.
24 **Aimaretti G**, Ambrosio MR, Di Somma C, *et al.* Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf)* 2004;**61**:320–6.
25 **Kelly DF**, Gonzalo IT, Cohan P, *et al.* Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid haemorrhage: a preliminary report. *J Neurosurg* 2000;**93**:743–52.
26 **Arafah BM**, Harrington JF, Madhoun ZT, *et al.* Improvement of pituitary function after surgical decompression for pituitary tumour apoplexy. *J Clin Endocrinol Metab* 1990;**71**:323–8.
27 **Randeva HS**, Schoebel J, Byrne J, *et al.* Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol (Oxf)* 1999;**51**:181–8.
28 **Shalet SM**, Toogood A, Rahim A, *et al.* The diagnosis of growth hormone deficiency in children and adults. *Endocr Rev* 1998;**19**:203–23.
29 **Growth Hormone Research Society (GRS)**. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency. Statement of the GRS workshop on adult GHD. *J Clin Endocrinol Metab* 1998;**83**:379–81.
30 **Murray RD**, Peacey SR, Rahim A, *et al.* The diagnosis of growth hormone deficiency (GHD) in successfully treated acromegalic patients. *Clin Endocrinol (Oxf)* 2001;**54**:37–44.
31 **Nicolson A**, Toogood AA, Rahim A, *et al.* The prevalence of severe growth hormone deficiency in adults who received growth hormone replacement in childhood. *Clin Endocrinol (Oxf)* 1996;**44**:311–16.
32 **Hoffman DM**, O'Sullivan AJ, Baxter RC, *et al.* Diagnosis of growth hormone deficiency in adults. *Lancet* 1994;**343**:1064–8.
33 **Jones SL**, Trainer PJ, Perry L, *et al.* An audit of the insulin tolerance test in adult subjects in an acute investigation unit over one year. *Clin Endocrinol (Oxf)* 1994;**41**:123–8.
34 **Hoeck HC**, Vestergoard P, Jakobson PE, *et al.* Test of growth hormone secretion in adults: poor reproducibility of the insulin tolerance test. *Eur J Endocrinol* 1995;**133**:305–12.
35 **Aimaretti G**, Corneli G, Razzore P, *et al.* Comparison between insulin-induced hypoglycaemia and growth hormone (GH)-releasing hormone + arginine as provocative tests for the diagnosis of GH deficiency in adults. *J Clin Endocrinol Metab* 1998;**83**:1615–18.
36 **Korbonits M**, Kaltsas G, Perry LA, *et al.* Hexarelin as a test of pituitary reserve in patients with pituitary disease. *Clin Endocrinol (Oxf)* 1999;**51**:369–75.
37 **Gasperi M**, Aimaretti G, Scarcello G, *et al.* Low dose hexarelin and growth hormone (GH)-releasing hormone as a diagnostic tool for the diagnosis of GH deficiency in adults: comparison with insulin-induced hypoglycemia test. *J Clin Endocrinol Metab* 1999;**84**:2633–7.
38 **Rahim A**, Toogood AA, Shalet SM. The assessment of growth hormone in normal young adult using a variety of provocative agents. *Clin Endocrinol (Oxf)* 1996;**45**:557–62.
39 **Gómez JM**, Espadero RM, Escobar-Jiménez F, *et al.* Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. *Clin Endocrinol (Oxf)* 2002;**56**:329–34.
40 **Toogood AA**, Jones J, O'Neill PA, *et al.* The diagnosis of severe growth hormone deficiency in elderly patients with hypothalamic-pituitary disease. *Clin Endocrinol (Oxf)* 1998;**48**:569–76.
41 **Pavord SR**, Girach A, Price DE, *et al.* A retrospective audit of the combined pituitary function test, using the insulin stress test, TRH and GnRH in a district laboratory. *Clin Endocrinol (Oxf)* 1992;**36**:135–9.
42 **Hurel SJ**, Thompson CJ, Watson MJ, *et al.* The short Synacthen and insulin stress tests in the assessment of the hypothalamic-pituitary-adrenal axis. *Clin Endocrinol (Oxf)* 1996;**44**:141–6.
43 **Plumpton FS**, Besser GM. The adrenocortical response to surgery and insulin-induced hypoglycaemia in corticosteroid treated and normal subjects. *Br J Surg* 1969;**56**:216–19.
44 **Stewart P**, Corrie J, Seckl J, *et al.* A rational approach for assessing the hypothalamo-pituitary-adrenal axis. *Lancet* 1988;i:1208–10.
45 **Clayton RN**. Short synacthen test versus insulin stress test for assessment of the hypothalamo-pituitary-adrenal axis: controversy revisited. *Clin Endocrinol (Oxf)* 1996;**44**:147–9.
46 **Soule SG**, Fahie-Wilson M, Tomlinson S. Failure of the short ACTH test to unequivocally diagnose long-standing symptomatic secondary hypoadrenalism. *Clin Endocrinol (Oxf)* 1996;**44**:137–40.
47 **Oelkers W**. Adrenal insufficiency. *N Engl J Med* 1996;**335**:1206–12.
48 **Littley MD**, Gibson S, White A, *et al.* Comparison of the ACTH and cortisol responses to provocative testing with glucagon and insulin-induced hypoglycaemia in normal subjects. *Clin Endocrinol (Oxf)* 1989;**31**:527–33.
49 **Baylis PH**, Cheetham T. Diabetes insipidus. *Arch Dis Child* 1998;**79**:84–9.
50 **De Herder WW**, Lamberts SW. Imaging of pituitary tumours. *Baillieres Clin Endocrinol Metab* 1995;**9**:367–89.
51 **Bates AS**, Bullivant B, Sheppard MC, *et al.* Life expectancy following surgery for pituitary tumours. *Clin Endocrinol (Oxf)* 1999;**50**:315–19.
52 **Nilsson B**, Gustavasson-Kadaka E, Bengtsson BA, *et al.* Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *J Clin Endocrinol Metab* 2000;**85**:1420–5.
53 **Monson JP**, Besser GM. Premature mortality and hypopituitarism. *Lancet* 2001;**357**:1972–3.
54 **Kohno H**, Kuromaru R, Ueyama N, *et al.* Premature mortality and hypopituitarism. *Lancet* 2001;**357**:1973–4.
55 **Erfurth EM**, Bengtsson BA, Christiansen JS, *et al.* Premature mortality and hypopituitarism. *Lancet* 2001;**357**:1972.
56 **Mukherjee A**, Murray RD, Columb B, *et al.* Acquired prolactin deficiency indicates severe hypopituitarism in patients with disease of the hypothalamic-pituitary (HP) axis. *Clin Endocrinol (Oxf)* 2003;**59**:743–8.
57 **Colao A**, Annunziato L, Lombardi G. Treatment of prolactinomas. *Ann Med* 1998;**30**:452–9.
58 **Lissett CA**, Peacey SR, Laing I, *et al.* The outcome of surgery for acromegaly: the need for a specialist pituitary surgeon for all types of growth hormone (GH) secreting adenoma. *Clin Endocrinol (Oxf)* 1998;**49**:653–7.
59 **Orth DN**. Cushing's syndrome. *N Engl J Med* 1995;**332**:791–803.
60 **Gittoes NJ**, Bates AS, Tse W, *et al.* Radiotherapy for non-function pituitary tumours. *Clin Endocrinol (Oxf)* 1998;**48**:331–7.
61 **de Boer H**, Blok GJ, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. *Endocr Rev* 1995;**16**:63–86.
62 **Carroll PV**, Christ ER, Bengtsson BA, *et al.* Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab* 1998;**83**:382–95.

63 **National Institute for Clinical Excellence**. Human growth hormone (somatotropin) in adults with growth hormone deficiency. *Technology Appraisal* 2003;**64**:4–7.
64 **Beshyah SA**, Johnston DG. Cardiovascular disease and risk factors in adults with hypopituitarism. *Clin Endocrinol (Oxf)* 1999;**50**:1–15.
65 **Vance ML**, Mauras N. Growth hormone therapy in adults and children. *N Engl J Med* 1999;**341**:1206–16.
66 **Shalet SM**, Trainer PJ. Pituitary hormone replacement. *Medicine* 2001;**29**:5–8.
67 **Statement from the Growth Hormone Research Society**. Critical evaluation of the safety of recombinant human growth hormone administration. *J Clin Endocrinol Metab* 2001;**86**:1868–70.
68 **Peacey SR**, Guo CY, Robinson AM, *et al*. Glucocorticoid replacement therapy: are patients over treated and does it matter? *Clin Endocrinol (Oxf)* 1997;**46**:255–61.
69 **Arlt W**, Allolio B. Adrenal insufficiency. *Lancet* 2003;**361**:1881–93.
70 **Howlett TA**. An assessment of optimal hydrocortisone replacement therapy. *Clin Endocrinol (Oxf)* 1997;**46**:263–8.
71 **Esteban NV**, Loughlin T, Yergey AL, *et al*. Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *J Clin Endocrinol Metab* 1991;**72**:39–45.
72 **Besser GM**, Jeffcoate WJ. Adrenal disease. *BMJ* 1976;i:448–51.
73 **Peacey SR**, Pope RM, Naik KS, *et al*. Corticosteroid therapy and intercurrent illness: the need for continuing patient education. *Postgrad Med J* 1993;**69**:282–4.
74 **Lamberts SW**, de Herder WW, van der Lely AJ. Pituitary insufficiency. *Lancet* 1998;**352**:127–34.
75 **Franklyn JA**. Diagnosis and treatment of thyrotropin deficiency. In: Lamberts S, ed. *The diagnosis and treatment of pituitary insufficiency*. Bristol: BioScientifica, 1997:99–111.
76 **Matsumoto AM**. Hormonal therapy of male hypogonadism. *Endocrinol Metab Clin North Am* 1994;**23**:857–75.
77 **Behre HM**, Kleisch S, Leifke E, *et al*. Long-term effect of testosterone therapy in bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 1997;**82**:2386–90.
78 **Torgerson DJ**, Bell-Seyer SE. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomised trials. *JAMA* 2001;**285**:2891–7.
79 **Armitage M**, Nooney J, Evans S. Recent concerns surrounding HRT. *Clin Endocrinol (Oxf)* 2003;**59**:145–55.
80 **Braunstein GD**. Androgen insufficiency in women: summary of critical issues. Review. *Fertil Steril* 2002;**77**(suppl 4):S94–9.
81 **Buchter D**, Behre HM, Kliesch S, *et al*. Pulsatile GnRH or human chorionic gonadotropin/human menopausal gonadotrophin as effective treatment for men with hypogonadotrophic hypogonadism: a review of 42 cases. *Eur J Endocrinol* 1998;**139**:298–303.
82 **Shoham Z**, Balen A, Patel A, *et al*. Results of ovulation induction using human menopausal gonadotropin or purified follicle-stimulating hormone in hypogonadotropic hypogonadism patients. *Fertil Steril* 1991;**56**:1048–53.
83 **Morris DV**, Abdulwahid NA, Armar A, *et al*. The response of patients with organic hypothalamic-pituitary disease to pulsatile gonadotropin-releasing hormone therapy. *Fertil Steril* 1987;**47**:54–9.
84 **Baylis PH**. Diabetes insipidus. *Medicine* 2001;**29**:13–15.