Hypopituitarism

Recognising new causes and reducing complications

ARIANNE N. SWEETING MB BS(Hons), BSc, GradDipPubHL, FRACP
ELIZABETH L. CHUA MB BS, PhD, FRACP

Hypopituitarism is becoming more common because of increasing recognition of novel causes of this condition. It is therefore essential that clinical practitioners are able to identify and manage this chronic disease to avoid life-threatening secondary adrenal insufficiency and maintain the patient's quality of life.

Hypopituitarism is defined as a deficiency of one or more of the anterior or posterior pituitary hormones. It is a rare but potentially life-threatening condition associated with increased mortality. Acute onset of hypopituitarism is a medical emergency due to a deficiency of adrenocorticotrophic hormone (ACTH), and glucocorticoid replacement is the most important aspect of initial resuscitation. Patients with hypopituitarism most commonly present with chronic subclinical nonspecific symptoms with a typical sequential loss of pituitary hormone

ENDOCRINOLOGY TODAY 2015; 4(2): 14-20

Dr Sweeting is an Endocrinology Fellow, Department of Endocrinology at Royal Prince Alfred Hospital and PhD Scholar, Sydney Medical School at The University of Sydney. Dr Chua is Director, Endocrinology & Metabolism Centre at Royal Prince Alfred Hospital and Clinical Associate Professor, Sydney Medical School at The University of Sydney, NSW.

Key points

- **Hypopituitarism can be a life-threatening condition due to secondary adrenal insufficiency.**
- **Hypopituitarism can present either acutely, with symptoms of sudden mass effect and secondary adrenal crisis, or more commonly as a subacute or chronic condition.**
- **Pituitary adenoma is the most common cause of hypopituitarism; however, immune-modulating therapy for metastatic melanoma is an increasingly recognised cause of autoimmune hypophysitis, particularly in Australia.**
- **Treatment involves adequate replacement of deficient hormones and long-term monitoring to prevent associated complications and improve quality of life.**
- **Ongoing education of the patient and their family, as well as clinical practitioners, forms a crucial component of management. Education includes glucocorticoid replacement therapy, appropriate sick-day management, how to administer intramuscular hydrocortisone, when to present to the emergency department, and the importance of wearing a MedicAlert or equivalent identification at all times.**

function, corresponding to the relative importance of the hormone for survival, with loss of ACTH occurring last.

The prevalence of hypopituitarism is estimated to be 45.5 per 100 000 people[1] but is likely to substantially rise because of increasing recognition of novel causes of hypopituitarism, including hypophysitis due to immune-modulating therapy for metastatic melanoma. It is therefore essential that clinical practitioners are able to identify and manage this chronic condition to avoid life-threatening secondary adrenal insufficiency and maintain the patient's quality of life. The case vignette in Box 1 illustrates the management of a young man with panhypopituitarism.

Clinical presentation

Hypopituitarism has a broad clinical spectrum of presentation, ranging from acute and catastrophic (due to secondary adrenal crisis causing life-threatening circulatory compromise or symptoms of sudden mass effect) to chronic nonspecific morbidity. The time period that defines acute compared with subacute or chronic is somewhat arbitrary, but typically acute will refer to hours rather than many days, weeks or months. Accordingly, due to its myridia of presentations that include a differing time course, a high index of clinical suspicion is required when considering hypopituitarism as a potential differential diagnosis. The common signs and symptoms associated with loss of specific pituitary hormone function are summarised in Box 2.

Mass effect symptoms can be either acute or chronic, and include progressive visual impairment due to optic nerve atrophy, bitemporal hemianopia, headaches and rarely oculomotor cranial nerve deficits.

Hypopituitarism presents more frequently as a chronic, subclinical condition with nonspecific morbidity relating to the degree and duration of hypopituitarism. A typical sequential pattern of anterior hormone loss is generally seen: gonadotrophins and growth hormone (GH) initially, followed by thyroid-stimulating hormone (TSH) and then ACTH.

Evidence of hormone hypersecretion (such as acromegaly or galactorrhoea) is suggestive of a pituitary adenoma, but can be associated with suppression of other pituitary hormones by the pressure effect of the mass lesion on surrounding normal pituitary cells. The presence of diabetes insipidus warrants further investigation for posterior pituitary pathology, and is frequently seen in lymphocytic hypophysitis. Postpartum absence of lactation or menses in pregnancy complicated by postpartum haemorrhage is highly suggestive of Sheehan's syndrome. Hypopituitarism and symptoms of mass effect due to infiltration will generally be accompanied by systemic signs and symptoms.

Causes of hypopituitarism

The most common cause of hypopituitarism is a pituitary adenoma, comprising almost two-thirds of all cases.[1] More novel causes of hypopituitarism, including traumatic brain injury and immunomodulatory therapy for metastatic melanoma, are increasingly

1. Case vignette

A 30-year-old man presented to the emergency department with sudden-onset severe headache on returning from his honeymoon overseas. On arrival to the emergency department, he was hypotensive with bitemporal hemianopia and right ptosis. An MRI showed a 22 mm pituitary mass with suprasellar extension impinging on the optic nerve and chiasm, and features consistent with haemorrhage into a large pituitary macroadenoma (see Figure below).

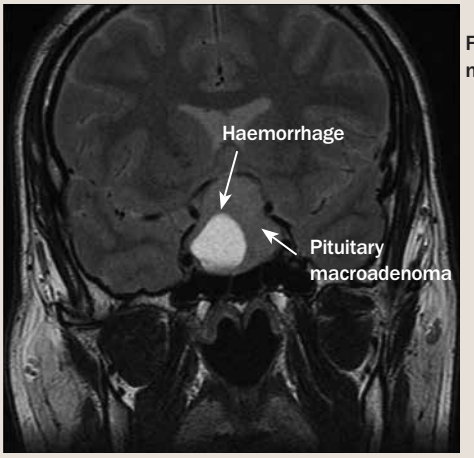

Figure. Pituitary macroadenoma.

Hormonal profile demonstrated low peripheral hormone levels with an inappropriately normal pituitary hormone level consistent with panhypopituitarism. Cortisol level was markedly low at 17 nmol/L (see Table below).

Hormone	Result	Reference range
Thyroid-stimulating hormone	0.294 mIU/L	0.270–4.200 mIU/L
Free thyroxine	9.9 pmol/L	12.0–25.0 pmol/L
Luteinising hormone	2.2 IU/L	1.7–8.6 IU/L
Follicle-stimulating hormone	3.4 IU/L	Men: 1.0–9.0 IU/L
Prolactin	2.0 ng/mL	2.0–16.0 ng/mL
Testosterone	5.4 nmol/L	Men 20–50 years: 6.0–29.0 nmol/L
Growth hormone	3.4 mU/L	18.0 mU/L or less
Cortisol	17 nmol/L	200–600 nmol/L

The patient underwent emergency surgical decompression with corticosteroid cover. Postoperatively, he had rapid and complete resolution of headache and all visual disturbances. Unfortunately, his panhypopituitarism did not resolve and he now requires lifelong hormone maintenance therapy.

2. Clinical presentation of hypopituitarism

ACTH deficiency
Lethargy, dizziness, postural hypotension, nausea and vomiting, weight loss, hypoglycaemia

TSH deficiency
Lethargy, bradycardia, weight gain, cold intolerance, hair thinning/loss, dry skin, slowed mentation

FSH/LH deficiency
Women: oligomenorrhoea/amenorrhoea, infertility, reduced libido, osteoporosis
Men: reduced libido, loss of muscle/bone mass, decreased beard/body hair growth

GH deficiency
Reduced muscle mass/strength, increased central fat accumulation, decreased quality of life

Abbreviations: ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinising hormone; TSH = thyroid-stimulating hormone.

3. Causes of hypopituitarism

Acute
Autoimmune: classic lymphocytic hypophysitis, anti-CTLA-4 therapy
Infarction: apoplexy, Sheehan's syndrome
Traumatic brain injury: acute insult, subarachnoid haemorrhage, cerebrovascular event
Drugs/medications: including use of opioids

Chronic
Sellar and suprasellar masses: pituitary tumours, craniopharyngiomas, Rathke's cleft cysts
Malignant infiltration: brain tumours, haematological malignancy (leukaemia, lymphoma), lung/breast metastases
Nonmalignant infiltration: granulomatous diseases (sarcoidosis, Wegener's granulocytosis, tuberculosis), Langerhans cell histiocytosis, haemochromatosis
Irradiation: cranial, pituitary, nasopharyngeal carcinomas
Medications: including use of supraphysiological corticosteroids
Congenital: pituitary hypoplasia/aplasia, genetic mutations

described. Causes of hypopituitarism are listed in Box 3 and some are discussed in more detail below.

Autoimmune

Autoimmune (lymphocytic) hypophysitis is an increasingly important cause of hypopituitarism. Lymphocytic hypophysitis may arise de novo or occur with other autoimmune conditions and is characterised by lymphocytic infiltration with resulting destruction of the pituitary. Historically, this condition was rare, more common in women and associated with the peripartum period. More recently, lymphocytic hypophysitis has been described as the pathophysiological mechanism of immunomodulatory therapy-induced hypopituitarism in people with metastatic melanoma, with a reported incidence of up to 17%.[2] In contrast to the typical pattern of anterior hormone loss seen in hypopituitarism, lymphocytic hypophysitis is frequently characterised by isolated ACTH deficiency.

Sheehan's syndrome

Sheehan's syndrome is classically associated with pregnancy and postpartum haemorrhage, causing severe hypotension and resultant pituitary ischaemia and hypopituitarism. This is a rare cause of hypopituitarism in developed countries; however, it should be considered in the setting of postpartum absence of lactation and menses, particularly if there is a clinical history of severe postpartum haemorrhage.

Apoplexy

Pituitary apoplexy results from haemorrhage or infarction of a pre-existing pituitary adenoma, commonly a macroadenoma, causing acute increased intrasellar pressure, mass effect symptoms and hypopituitarism. Most cases (60 to 80%) occur spontaneously; however, reported precipitating factors include closed head trauma, hypotension or hypertension, previous cranial irradiation, use of anticoagulants and dopamine agonists, and dynamic pituitary function testing.[3]

Traumatic brain injury

Studies have reported that up to 35% of patients develop hypopituitarism following a traumatic brain injury, occurring either at presentation or six months post injury.[4] Subarachnoid haemorrhage is another potential cause of hypopituitarism. Similar to the pattern of hypopituitarism in lymphocytic hypophysitis, traumatic brain injury is frequently associated with isolated ACTH deficiency.

Opioids

Opioids have multiple acute and chronic effects on several endocrine axes, primarily mediated via κ-receptors in the hypothalamus and pituitary.[5] Opioids are associated with both isolated reversible ACTH deficiency and gonadal hormone deficiency, with time to recovery depending on the duration of opioid exposure.

Sellar and suprasellar masses

Pituitary adenomas are the most common cause of hypopituitarism and are generally benign. Most adenomas are nonfunctioning (reported rates of 27.4 to 57.3%) or prolactinomas (9.3 to 39.0%).[6] Pituitary carcinoma is exceedingly rare. Hypopituitarism may be apparent at presentation due to mass effect of the adenoma or be iatrogenic following pituitary surgery.

Craniopharyngiomas are the most common suprasellar tumours and are associated with panhypopituitarism and diabetes insipidus. Other suprasellar tumours include Rathke's cleft cysts and dermoid, epidermoid and arachnoid cysts.

Infiltration

Several systemic conditions are associated with hypophyseal infiltration, granulomatous hypophysitis and hypopituitarism. Sarcoidosis is complicated by central nervous system involvement in 5% of cases,[7] commonly manifesting as diabetes insipidus and hypopituitarism. Wegener's granulocytosis, Langerhans cell histiocytosis and haemochromatosis are also associated with hypopituitarism.

Neurological neoplasms such as gliomas and primary haematological malignancies, such as leukaemia and lymphoma, can lead to hypopituitarism – either via direct infiltration and destruction or secondarily due to treatment sequelae (surgery or cranial irradiation). Metastatic deposits to the pituitary are another important cause of hypopituitarism; most commonly associated with advanced breast and lung malignancy.

Cranial irradiation

Cranial radiotherapy for tumours or haematological malignancy distant to the hypothalamic–pituitary axis is associated with significant rates of irreversible and progressive hypopituitarism. A meta-analysis reported a point prevalence of any degree of hypopituitarism of 66%, most commonly GH deficiency,[8] possibly due to selective radiosensitivity of this axis in patients receiving cranial radiation therapy.[9] Improvement in survival rates for childhood malignancy will significantly increase the prevalence of this condition. The severity and likelihood of hypopituitarism positively correlates to the dose of radiotherapy and duration of follow up, underscoring the need for long-term monitoring.

Hypopituitarism is also a well-described complication of radiotherapy (either stereotactic or fractionated) for pituitary adenomas.

Investigations

A diagnosis of hypopituitarism is made biochemically based on basal peripheral and pituitary hormone levels and dynamic pituitary function testing if indicated (Box 4). Pituitary MRI is used to determine pathophysiology and presence of local invasion/compression and is generally undertaken once hypopituitarism is confirmed.

Biochemistry

The combination of low basal peripheral hormones and inappropriately low to normal pituitary hormones is suggestive of hypopituitarism. Dynamic multiple pituitary stimulation testing may also be required to definitively confirm ACTH or GH deficiency and should be undertaken in a specialised endocrine centre. Evidence suggests that secondary adrenal insufficiency can be excluded at early morning cortisol concentrations of above 450 nmol/L, and is likely at levels below 100 nmol/L.[10] If cortisol concentrations are within the equivocal range, referral of the patient to an endocrine centre for a stimulation test, such as an insulin tolerance test, is recommended to determine if there is an appropriate cortisol rise to stress, in the absence of contraindications (e.g. seizures or ischaemic heart disease). Adequate response is defined as a peak cortisol concentration of above 550 nmol/L that has doubled from baseline in response to hypoglycaemia (blood glucose level <2.2 mmol/L). A short Synacthen test may also be undertaken with the caveat that it may fail to detect central adrenal insufficiency of recent onset as the adrenal glands have not yet atrophied. GH deficiency should also be confirmed by dynamic testing, unless there is biochemical evidence of panhypopituitarism and low levels of insulin-like growth factor-1. A GH level of 3 μg/L or less during insulin tolerance testing confirms the diagnosis.

The diagnosis of TSH deficiency is made when free thyroxine levels are decreased in the setting of a low or inappropriately normal TSH level. In contrast to primary hypothyroidism, TSH measurement alone is insufficient for a diagnosis of central hypothyroidism. Gonadotrophin deficiency in premenopausal women is confirmed by the presence of oligoamenorrhoea, low oestrogen levels and inappropriately low luteinising hormone and follicle-stimulating hormone levels, and in postmenopausal women by low luteinising hormone and follicle-stimulating hormone levels. In men, confirmation of low basal testosterone levels, performed in the morning, and low or inappropriately normal gonadotrophin levels is diagnostic (see Figure 1).

Diabetes insipidus (antidiuretic hormone deficiency) is confirmed in the presence of polyuria and polydipsia, elevated serum sodium and serum osmolality, and inappropriately low urine osmolality. A water deprivation test may be required if the serum sodium level is within the normal range or there is doubt as to whether diabetes insipidus is of nephrogenic or central origin. The absence of an increase in urine osmolality despite a rise in serum sodium levels

4. Work up for hypopituitarism in primary care settings

ACTH/adrenal deficiency
Early morning ACTH: low or inappropriately normal
Early morning cortisol: low (<100 nmol/L)

TSH/thyroid deficiency
TSH: low or inappropriately normal
Free thyroxine: low

Gonadotrophin/ovarian/testicular deficiency
LH/FSH: low or inappropriately normal
Oestradiol: low
Early morning testosterone: low

GH deficiency
GH: low or inappropriately normal
IGF-1: low or normal for age-specific reference range

Prolactin
Low or may be slightly elevated secondary to pituitary stalk compression

Abbreviations: ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor-1; LH = luteinising hormone; TSH = thyroid-stimulating hormone.

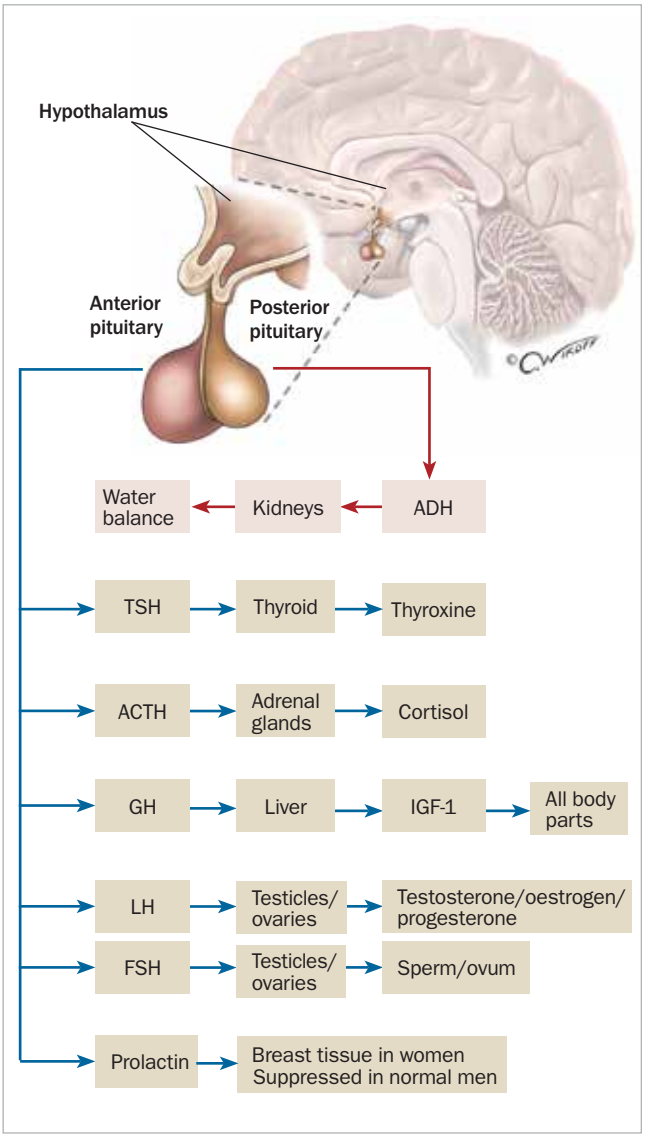

Figure 1. Pituitary hormonal axes in men and women.
Abbreviations: ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; IGF-1 = insulin-like growth factor-1; LH = luteinising hormone; TSH = thyroid-stimulating hormone.

and osmolality after water restriction, followed by a rise in urine osmolality and fall in urine output after administration of desmopressin (exogenous antidiuretic hormone), is diagnostic of central diabetes insipidus.

Other investigations (e.g. measurement of serum levels of angiotensin-converting enzyme and chest radiograph if sarcoid is suspected, iron studies, full blood count and bacterial/fungal cultures in the setting of immune deficiency [e.g. HIV infection] if indicated) will be guided by the probable diagnosis and systemic signs. Pituitary biopsy to confirm underlying pathophysiology is rarely required but may be considered to differentiate infiltrative conditions and occasionally hypophysitis.

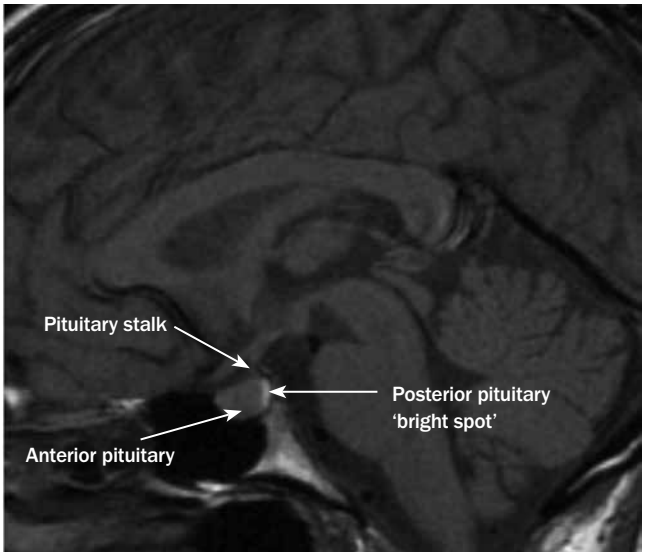

Figure 2. MRI of a normal pituitary gland (T1 image).

Pituitary MRI

MRI of the pituitary windows with gadolinium enhancement is the preferred imaging modality for assessment of pituitary pathology and also guides surgical management. Pituitary macroadenomas may be associated with invasion into the cavernous sinus or haemorrhage and necrosis (suggested by heterogeneous enhancement post-gadolinium). Lymphocytic hypophysitis and other inflammatory conditions are associated with diffuse thickening and enhancement of the pituitary stalk and loss of the posterior 'bright spot'. Infiltration may demonstrate local invasion into the cavernous sinus, asymmetrical stalk/gland thickening and large mass lesions. Deviation of the stalk, haemorrhage or infarction and empty sella are suggestive of a traumatic lesion; skull base fracture may or may not also be present. An MRI of a normal pituitary for comparison is shown in Figure 2.

Management

Management depends on whether the hypopituitarism is acute or chronic. Acute management includes immediate administration of intravenous or intramuscular hydrocortisone (generally 100 mg immediately then 100 mg eight hourly or 50 mg six hourly) and fluid resuscitation.

Restoration of pituitary function should be a priority if there is potential for reversibility, and surgical decompression is required for symptoms of mass effect. Appropriate and timely hormone replacement is essential, as is education and monitoring for long-term complications associated with hypopituitarism.

Surgery

Transsphenoidal resection is the preferred surgical approach and is indicated for symptomatic tumours (including functioning adenomas), for acute presumably reversible hypopituitarism due to a resectable lesion and for decompression in the presence of mass

effect symptoms. In a large study of patients undergoing transsphenoidal resection for nonfunctioning pituitary adenomas, hypopituitarism improved in 50% of patients postsurgery and worsened in 2%.[11] In contrast, a recent Australian study demonstrated postoperative hormone recovery in just over one-third of cases.[12] An important exception is prolactinomas, in which primary medical therapy with dopamine agonists should be first-line management.

Hormone replacement

Chronic glucocorticoid maintenance therapy should preferably consist of oral glucocorticoids administered at a dose and timing that mimics the normal cortisol production rate and pattern. As patients with secondary adrenal insufficiency may still have some endogenous glucocorticoid production, the replacement dose is generally lower than in those with primary adrenal insufficiency. A range of possible glucocorticoid preparations and dosages may be used. Hydrocortisone or cortisone acetate administered in two divided daily doses, with the larger dose in the morning (e.g. hydrocortisone 12 mg) and the second dose mid-afternoon (e.g. hydrocortisone 8 mg), mirrors the diurnal pattern. Weight-based dosing for hydrocortisone and cortisone acetate is recommended in Australia.[13]

There is no laboratory test to assess the adequacy of glucocorticoid replacement and thus clinical assessment is key. Inadequate replacement may be associated with reduced energy levels, postural hypotension, nausea and abdominal pain, whereas over-replacement will lead to Cushingoid features and osteoporosis. The patient and their family should be educated on appropriate sick-day management, including instructions on glucocorticoid dose increases when unwell, how to administer intramuscular hydrocortisone and when to present to the emergency department, and this should be discussed at each visit. The patient should wear a MedicAlert at all times.

In central hypothyroidism, TSH is not used as a guide for titration of thyroxine dose. Thyroxine replacement should also be given in the morning on an empty stomach aiming for free thyroxine levels at the upper limit of normal. A lower initial dose of 25 to 50 µg daily is advised in older patients with cardiovascular disease. Glucocorticoid replacement, if ACTH deficient, must be achieved before commencing thyroxine to avoid precipitating adrenal crisis, as thyroxine increases glucocorticoid metabolism.

Hormone replacement therapy, preferably transdermal administration, should be initiated in premenopausal women aiming for oestrogen levels in the normal range and be discontinued by 50 to 55 years of age.[14] In men, testosterone replacement should aim to achieve a trough level in the mid-normal range. Before commencing testosterone therapy, screening for obstructive sleep apnoea and measurement of baseline haematocrit and prostate-specific antigen levels should be undertaken and reviewed annually.

Hypopituitarism associated with infertility can be treated with ovulation induction using gonadotrophin therapy, achieving pregnancy rates of 47%.[15] Exogenous testosterone therapy should be avoided in a man desiring fertility as this may lead to azoospermia and infertility; however, this can be considered after sperm banking. Alternatively, human chorionic gonadotrophin injections can be used.

Adult GH replacement is not currently PBS listed. Studies are conflicting but overall appear to demonstrate improvements in body composition, lipid profile and quality of life with use of GH replacement in adults with hypopituitarism; however, concerns over potential increased risk of cardiovascular disease or malignancy persist with use of this therapy.[14]

Diabetes insipidus is managed with either intranasal or (preferably) oral desmopressin titrated to the patient's symptoms, with early morning serum sodium and osmolality measurements useful in guiding ongoing treatment.

Monitoring

Following initial dose titration, lifelong surveillance of the patient by both the endocrinologist and GP is required. Progress MRI or formal visual field testing should be undertaken if indicated, for example, in the setting of a macroadenoma or progressive hormone deficits. Associated complications, such as diabetes, cardiovascular disease, dyslipidaemia and osteoporosis, should also be screened for. Studies have shown increased mortality in people with hypopituitarism, generally due to cardiovascular disease. Moreover, there is also an association between the glucocorticoid replacement dose and mortality in patients with hypopituitarism.[16] Although a causal relationship is yet to be established, it seems prudent to avoid excessive maintenance doses, using the lowest glucocorticoid dose that keeps the patient well, but to respond quickly with stress doses during illness to avoid adrenal crisis.

Conclusion

Hypopituitarism encompasses a diverse spectrum of conditions and clinical presentations, and thus its prevalence has long been underestimated. The increasing recognition of novel causes of hypopituitarism will significantly increase the prevalence of this disease, and clinical practitioners should be able to identify and manage patients with this condition.

Acute-onset hypopituitarism is a life-threatening condition requiring immediate glucocorticoid replacement and resuscitation, with potential for normalisation of pituitary function in certain circumstances. Acute secondary adrenal crisis remains a lifelong risk in these patients, which can be prevented by a clear sick-day management plan for glucocorticoid replacement and continual education of the patient and their family, as well as clinical practitioners. Hypopituitarism is an irreversible chronic disease requiring long-term hormone replacement and surveillance to minimise complications associated with both the disease itself and inadequate and/or supraphysiological hormone replacement. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

COMPETING INTERESTS: None.

Hypopituitarism
Recognising new causes and reducing complications

ARIANNE N. SWEETING MB BS(Hons), BSc, GradDipPubHL, FRACP; **ELIZABETH L. CHUA** MB BS, PhD, FRACP

References

1. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol 2001; 55: 735-740.
2. Dillard T, Yedinak CG, Alumkal J, Fleseriu M. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. Pituitary 2010; 13: 29-38.
3. Nawar RN, AbdelMannan D, Selman WR, Arafah BM. Pituitary tumor apoplexy: a review. J Intensive Care Med 2008; 23: 75-90.
4. Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla GK, Ghigo E. Hypopituitarism. Lancet 2007; 369: 1461-1470.
5. Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. Endocrine Rev 2010; 31: 98-132.
6. Ezzat S, Asa SL, Couldwell WT, et al. The prevalence of pituitary adenomas: a systematic review. Cancer 2004; 101: 613-619.
7. Bullmann C, Faust M, Hoffmann A, et al. Five cases with central diabetes insipidus and hypogonadism as first presentation of neurosarcoidosis. Eur J Endocrinol 2000; 142: 365-372.
8. Appelman-Dijkstra NM, Kokshoorn NE, Dekkers OM, et al. Pituitary dysfunction in adult patients after cranial radiotherapy: systematic review and meta-analysis. J Clin Endocrinol Metab 2011; 96: 2330-2340.
9. Darzy KH, Shalet SM. Hypopituitarism following radiotherapy. Pituitary 2009; 12: 40-50.
10. Grossman AB. Clinical review: the diagnosis and management of central hypoadrenalism. J Clin Endocrinol Metab 2010; 95: 4855-4863.
11. Nomikos P, Ladar C, Fahlbusch R, Buchfelder M. Impact of primary surgery on pituitary function in patients with non-functioning pituitary adenomas -- a study on 721 patients. Acta Neurochirurgica 2004; 146: 27-35.
12. Caputo C, Sutherland T, Farish S, McNeill P, Ng KW, Inder WJ. Gender differences in presentation and outcome of nonfunctioning pituitary macroadenomas. Clin Endocrinol 2013; 78: 564-570.
13. Therapeutic Guidelines: endocrinology. Version 5. Melbourne: Therapeutic Guidelines Limited 2014.
14. Toogood AA, Stewart PM. Hypopituitarism: clinical features, diagnosis, and management. Endocrinol Metab Clin North Am 2008; 37: 235-261.
15. Hall R, Manski-Nankervis J, Goni N, Davies MC, Conway GS. Fertility outcomes in women with hypopituitarism. Clin Endocrinol 2006; 65: 71-74.
16. Zueger T, Kirchner P, Herren C, et al. Glucocorticoid replacement and mortality in patients with nonfunctioning pituitary adenoma. J Clin Endocrinol Metab 2012; 97: E1938-1942.