Anaesthesia and pituitary disease

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Key points
Pituitary is a master endocrine gland that regulates the activities of all other endocrine glands in the body.
Presentation of pituitary disease is either by direct effects of hormone hyper-/ hyposecretion or due to mass effect of the enlarging gland.
Pituitary diseases have anaesthetic implications, such as a challenging airway, obstructive sleep apnoea, and associated endocrine disease.
Majority of pituitary surgery is now performed via the transsphenoidal approach as it has fewer incidence of complications.
A multidisciplinary approach is important in managing patients with pituitary disease.

Pituitary gland is a master endocrine gland of the neuro-endocrine axis, having a central role in governing hormonal homeostasis, maintaining the reproductive cycle, and coordinating the activity of other glands. Pituitary disease is common, and a thorough knowledge of the anatomy, physiology, and pathology of the pituitary is required to appropriately manage such patients for surgery.

Anatomy
The pituitary gland occupies the sella turcica of the sphenoid bone at the base of the skull, the roof of which is created by an incomplete fold of dura, the diaphragma sella, through which passes the pituitary stalk. The fossa is limited posteriorly by the clivus of the sphenoid and anteriorly and inferiorly by the sphenoidal air sinuses. The pituitary is related to the third ventricle, hypothalamus, and visual pathways anteriorly and inferiorly by the sphenoidal air sinuses. The pituitary is related to the third ventricle, hypothalamus, and visual pathways superiorly, and the cranial nerves III, IV, V, and VI, cavernous sinus and to the internal carotid arteries laterally. These structures can be damaged during pituitary surgery, leading to cranial nerve palsies, visual field defects, major haemorrhage, and cerebrospinal fluid (CSF) leaks. The gland weighs 500–900 mg and measures about 15 × 10 × 6 mm in an adult.1

Anatomically, the human pituitary has two lobes: anterior and posterior. The anterior lobe (adenohypophysis) constitutes two-thirds of the volume of the gland and the posterior lobe (neurohypophysis) constitutes the remainder. The adenohypophysis is further divided into pars distalis, pars tuberalis, and pars intermedia. The neurohypophysis is divided into pars nervosa and the infundibulum. Developmentally, the anterior lobe originates from Rathke’s pouch and the posterior lobe from neural crest cells. The two pituitary lobes function as separate endocrine organs, their cell populations classified by electron microscopic appearances, and functionality. The neurohypophysis is anatomically continuous with the hypothalamus via the hypothalamo-hypophyseal nerve tract. The pituitary gland lies outside the blood–brain barrier, but maintains anatomical and functional connections with the brain.2

The blood supply to the hypothalamo-pituitary axis is complex. The hypothalamus receives its blood supply from the circle of Willis, while the neurohypophysis and adenohypophysis receive blood from the inferior hypophyseal artery (IHA) and superior hypophyseal artery (SHA), respectively, which are branches of the internal carotid. The SHA and the IHA anastomose with each other forming a vascular plexus that encircles the gland. The capillary plexus of the IHA forms ‘short’ portal veins that drain into the anterior pituitary as well as the dural venous sinuses. The ‘long’ portal veins are formed from the capillary plexus of the SHA that supplies the nerve endings of the neurosecretory cells in the median eminence of the hypothalamus in addition to the adenohypophysis. The hypothalamic hormones are released into the long portal veins, through which they are transported to the anterior lobe. Here, the portal veins form a secondary capillary network into which the anterior pituitary hormones are secreted. Venous drainage from the gland is to the cavernous sinuses and into the internal jugular vein via the petrosal sinuses.2

Physiology
The pituitary gland produces several hormones (Table 1); some having a continuous pattern of release, but most are released in bursts every 1–3 h. Plasma levels of anterior pituitary hormones fluctuate in a diurnal manner, the exact mechanism of which is not known, rising in the early hours of the morning.3 In women, the levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) vary during the menstrual cycle.

Regulation of pituitary function
The posterior pituitary is regulated directly by the hypothalamic axons which project to it and...
synapse with its cells. The anterior pituitary is regulated by hypothalamic tropic hormones that reach it via the portal venous system. The hypothalamic influence is mainly stimulatory, which is in turn regulated by negative feedback control exerted at the pituitary and hypothalamic level, the classical example being the feedback regulation of thyroid-stimulating hormone (TSH) by the thyroid hormones (Fig. 1).

**Pituitary pathology**

**Adenomas of the adenohypophysis and clinical lesions of the pituitary gland**

Pituitary tumours present clinically in one of three ways: hormone hypersecretion syndromes, hormone hyposecretion, or mass effects, although they are frequently an incidental finding on CT, or at autopsy. The mode of presentation is governed largely by the tumour size and cell type. Macroadenomas are greater than 10 mm in diameter, and present with the consequences of a local mass effect, commonly headache and subtle visual field defects. Larger tumours can cause hypopituitarism, cranial nerve palsies, and hydrocephalus due to blockage of third ventricle outflow. Therapeutic options include medical therapy (prolactinomas), or surgical decompression, occasionally supplemented with radiotherapy. Microadenomas are <10 mm in diameter and present with symptoms of hormonal excess, the classic example being Cushing’s disease [excess of adrenocorticotropic hormone (ACTH)] or very rarely thyrotoxicosis (excess of TSH).

**Hormone hypersecretion syndromes**

**Acromegaly**

Acromegaly, derived from the Greek acron (extremity) and megalé (great), is a chronic, progressive, multisystem disease caused by an excess of growth hormone (GH) after puberty. It results from the hypersecretion of GH from a functioning pituitary macroadenoma; therefore, patients present with local mass effect and excess of

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**Table 1** Pituitary hormones and their functions

<table>
<thead>
<tr>
<th>Hormone and site of production</th>
<th>Target organ and function</th>
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<tbody>
<tr>
<td>Anterior pituitary ACTH pars distalis</td>
<td>Adrenal glands: stimulates the glands to produce glucocorticoids and aldosterone</td>
</tr>
<tr>
<td>GH pars distalis</td>
<td>Musculoskeletal system: anabolic effects on bone and muscle. Promotes lipolysis, increases free fatty acid levels, and impairs glucose utilization and cellular sensitivity to insulin</td>
</tr>
<tr>
<td>Prolactin pars distalis</td>
<td>Mammary glands: stimulates the glands to produce milk</td>
</tr>
<tr>
<td>FSH and LH pars tuberalis</td>
<td>Ovary: inhibits the actions of gonadotropins on the ovary</td>
</tr>
<tr>
<td>TSH pars tuberalis</td>
<td>Thyroid: stimulate the testes to produce sperm and testosterone, and the ovaries to produce eggs and oestrogen</td>
</tr>
<tr>
<td>Beta-melanocyte-stimulating hormone pars intermedia</td>
<td>Skin: causes increased pigmentation</td>
</tr>
<tr>
<td>Endorphins and encephalins pars intermedia</td>
<td>Brain and immune system: inhibits pain sensations</td>
</tr>
<tr>
<td>Posterior pituitary Oxytocin</td>
<td>Kidneys: regulates the amount of water excreted by the kidneys and maintains water balance in the body</td>
</tr>
<tr>
<td></td>
<td>Uterus: contracts the uterus during childbirth and immediately after delivery</td>
</tr>
<tr>
<td></td>
<td>Mammary glands: stimulates contractions of the milk ducts in the breast leading to the let-down reflex, which moves milk to the nipple in lactating women</td>
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**Fig 1** Control of thyroxine secretion: a negative feedback loop. Steps involved in the stimulation of hormone secretion by the thyroid gland, showing negative feedback at each step, both by the thyroid hormones (left) and other related hormones (right). GH. It is an insidious onset disease of middle age, and is typically well advanced at the time of diagnosis.

Acromegaly presents a variety of challenges to the anaesthetist. Airway maintenance and manual ‘bag and mask’ ventilation is usually straightforward. Laryngoscopy and tracheal intubation may be more difficult, due to a combination of macroglossia, macroglossia, and expansion of upper airway soft tissues; however, tracheal intubation is achievable with standard techniques such as external laryngeal pressure and the use of a gum elastic bougie or airway exchange catheter. Awake fibreoptic intubation is
increasingly regarded as the favoured solution for difficult intubation in these patients. Up to 70% of patients will have significant obstructive sleep apnoea (OSA) as a result of soft tissue enlargement of the upper airway. This is associated with airway difficulties, cardiac instability, and postoperative cardiorespiratory failure. Respiratory function may be additionally compromised by kyphoscoliosis and proximal myopathy. Patients with acromegaly may have refractory hypertension with eccentric left ventricular hypertrophy, ischaemic heart disease, arrhythmias, heart block, cardiomyopathy, and bi-ventricular dysfunction. Preoperative transthoracic echocardiography is useful to assess left ventricular size and performance, and to estimate pulmonary pressures. Excess peripheral soft tissue deposition may make venous cannulation difficult and increases the risk nerve entrapment syndromes; meticulous attention to theatre positioning is therefore required. Diabetes mellitus and other endocrine pathologies may be present. Postoperative care for these patients should be provided in a high dependency or intensive care setting, particularly in patients with established sleep apnoea.5

Cushing’s disease

The term Cushing’s disease is reserved for an excess of glucocorticoid due to hypersecretion of ACTH from a pituitary corticotroph adenoma, the term Cushing’s syndrome being applied to a non-specific state of chronic glucocorticoid excess regardless of cause. Surgical excision is the definitive management, but medical treatment may reverse much of the effects of excess glucocorticoid and considerably reduces perioperative risk. The typical habitus of Cushing’s syndrome is one of truncal obesity, moon facies and thin extremities. Friable skin and thin peripheral veins make venous access difficult to establish and there is a high risk of subcutaneous extravasation. Atrophic skin is easily damaged with handling. Central venous cannulation is difficult due to cervical obesity and supraclavicular fat pads, making ultrasound guidance invaluable. There is an increased risk of blood-borne infections with central access. Osteoporotic joints, especially vertebral, may render regional analgesia more difficult and make patient handling and positioning more hazardous. Exophthalmos secondary to retrobulbar deposits of fat is seen in a third of patients with Cushing’s disease, and care must be taken to avoid corneal injury.

Patients may have a difficult airway due to obesity and an increased incidence of OSA. A large ‘buffalo hump’ may interfere with supine positioning on the operating table and impede both airway management and surgical access. Respiratory function may be impaired in the postoperative period, particularly in patients with proximal muscle wasting, and these patients need high dependency or intensive care in the immediate postoperative period.

More than 80% of patients with Cushing’s disease have systemic hypertension, which may be refractory to standard treatment. Long-standing disease is associated with eccentric left ventricular hypertrophy and diastolic ventricular dysfunction. Haemodynamic instability during induction is common, and invasive arterial pressure monitoring under local anaesthesia beforehand is advisable. There is a significantly higher risk of perioperative venous thromboembolic disease.

Glucose intolerance is seen in almost two-thirds of patients with Cushing’s disease, half of whom will have frank diabetes. Particular care is needed in the postoperative period for patients undergoing potentially curative resection of ACTH secreting tumours, since glucose intolerance may resolve rapidly. There is an increased incidence of peptic ulceration, and non-steroidal anti-inflammatory drugs should be used with caution.6

Prolactinomas

Prolactinomas are the commonest functioning pituitary adenomas, accounting for ~30% of all pituitary tumours. Hyperprolactinaemia causes galactorrhoea and menstrual dysfunction in women, and secondary hypogonadism, reduced libido, and erectile dysfunction in men. Surgery is indicated only if first-line medical management with dopamine agonists like bromocriptine and cabergoline fails, or is not tolerated. The pathophysiological consequences of hyperprolactinaemia do not affect perioperative care.

Hormone hyposecretion

The endocrine hyposecretion syndromes associated with pituitary disease include adrenocortical insufficiency, hypothyroidism, and diabetes insipidus (DI). Posterior lobe dysfunction is rare, although a relatively frequent complication of surgical resection.

Adrenocortical insufficiency can be a life-threatening condition, particularly in patients with acute concurrent illness. However, in this context, the adrenocortical insufficiency is due to pituitary disease, the renin–angiotensin–aldosterone axis is preserved, so that in comparison with Addison’s disease, fluid and electrolyte abnormalities are less severe. In the acute setting, patients require i.v. hydrocortisone, together with saline resuscitation, and possibly glucose.

Pituitary-related hypothyroidism is usually less severe than primary thyroid failure. Nevertheless, anaesthesia and surgery in patients with untreated hypothyroidism carries a high mortality. Patients show increased sensitivity to and reduced metabolism of all classes of anaesthetic drugs, and doses should be reduced and titrated against effect. Emergence from anaesthesia may be very prolonged, necessitating postoperative respiratory support. The normal ventilatory responses to hypcapnia and hypoxia are obtunded and perioperative hypothermia is common. Clinical response to thyroid replacement therapy may take 10 days or, although more rapid correction can be achieved with i.v. l-iodothyronine (T3), there is a significant risk of precipitating myocardial ischaemia and heart failure.

Central DI is the result of failure of secretion of ADH. It is treated with desmopressin, a synthetic analogue of ADH that has a longer half life and which lacks the vasoconstricting properties of the endogenous hormone. Although desmopressin is usually administered orally or intra-nasally, after operation it can be given as a subcutaneous or intra-muscular injection. Failure to secrete
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Oxytocin only becomes clinically evident during and after childbirth, and is not relevant in the acute setting.7

Pituitary surgery

Surgery is the primary treatment modality for some pituitary tumours or may become indicated due to failure or intolerance of medical management.

Surgical approach

The vast majority of surgical resections of pituitary adenomas are now performed extracranially, via the transsphenoidal approach, with transcranial resection being reserved for occasions in which the trans-sphenoidal approach has failed, the tumour is large or when there is little or no intrasellar tumour. The advantages of the trans-sphenoidal approach are minimal surgical trauma and blood loss, direct access to the gland, and avoidance of the generic hazards of a craniotomy. Complications of transsphenoidal surgery include persistent CSF rhinorrhoea and the associated risk of post-operative meningitis, panhypopituitarism, transient DI, vascular damage, cranial nerve injury, cerebral ischaemia, and stroke as a result of vasospasm or thromboembolism.8 Deliberate nasal septum fracture is required for transsphenoidal transnasal approach, and to minimize nasal bleeding, mucosal vasoconstriction is achieved by using a topical anaesthetic and a vasoconstrictor. The use of epinephrine and/or cocaine as vasoconstrictors may cause an exaggerated hypertensive response in patients with Cushing’s disease and co-phenylecaine (5% lidocaine 0.5% phenylephrine) is a suitable alternative.

Preoperative considerations for transsphenoidal surgery

All patients need an appropriate preoperative assessment and endocrinology review to define the extent of pituitary dysfunction. Current medications should be reviewed, and hormonal and antihypertensive therapy should be continued. Although MRI is the preferred imaging modality for surgical planning, CT can be used to exclude hydrocephalus. Visual field defects should be mapped and documented. Patients should be counselled regarding invasive monitoring, and warned of the postoperative nasal obstruction caused by the use of nasal packs and reassured accordingly.9

Intubation

In cases of anticipated difficult intubation, awake orotracheal fibreoptic intubation is the technique of choice. There is an unpredictable nature of difficult tracheal intubation in patients with acromegaly. The airway in Cushing’s is not difficult per se, but obesity may render it difficult. The airway is obscured with the surgical approach and further restricted by an operating microscope, endoscopes, and portable X-ray imaging C-arms. The oropharynx is packed with saline-soaked gauze to stabilize the tracheal tube and to protect the lower airway from accumulation of blood and secretions.

Anaesthetic technique

The choice of anaesthetic technique depends on the patients’ comorbidities and past anaesthetic history. Antibiotics and i.v. hydrocortisone are administered during induction. Periods of intense surgical stimulation occur during deliberate nasal septal fracture and breaching of the sphenoid for access to the fossa. Inhalation or i.v. anaesthesia is acceptable for pituitary surgery. Short acting agents such as remifentanil are ideal, allowing intraoperative haemodynamic control and facilitating rapid recovery. This enables neurological assessment and avoids problems with postoperative airway management. Lumbar drains maybe inserted before operation to allow injection of small volumes of saline or air to promote descent of the tumour into the operative field. The same effect can also be achieved by controlled hypercapnoea. Pain relief is by intraoperative paracetamol, which is useful for its opioid-sparing effects. The use of non-steroidal anti-inflammatory drugs remains controversial in neurosurgery due to links with postoperative haematomas. Postoperative analgesia is provided by titrated doses of long-acting opioids towards the end of surgery and in the post-anaesthesia care unit. Postoperative nausea and vomiting is common after any neurosurgery and routine pharmacological prophylaxis is advised.10

Intraoperative complications

Venous air embolism is uncommon despite the semi-sitting position. Haemorrhage from damage to the carotid artery is a rare but potentially serious complication.

Postoperative course

All patients who undergo transsphenoidal pituitary surgery should be nursed in a high dependency area after operation due to a risk of airway obstruction. Patients with history of sleep apnoea are at greater risk. Nasal continuous positive airway pressure (CPAP) is contraindicated after transsphenoidal surgery due to the risk of tension pneumocephalus. The level of consciousness, eye movements, visual fields, and acuity should be tested frequently and any deterioration discussed with the surgeon, and radiological investigation and/or re-exploration considered.11
Postoperative neuroendocrine abnormalities can occur after pituitary surgery. DI usually develops within the first 24 h, and resolves spontaneously in about a week. If persistent, DI is treated with parenteral or intranasal desmopressin. Hyponatremia can be caused by excess desmopressin administration or, rarely due to syndrome of inappropriate ADH secretion. It is managed with fluid restriction to 500–1000 ml a day. Normal replacement therapy will be required in all patients after operation. Steroid replacement therapy is administered in a standardized reducing regime, and additional replacement therapy is defined by patients’ postoperative hormonal function. Close liaison with endocrinologists should be sought for all replacement therapy.

Pituitary apoplexy

The term refers to acute haemorrhagic infarction of a gland whose blood supply is previously compromised by a tumour or pregnancy. It can be caused by obstetric haemorrhage (Sheehan syndrome), major surgery, head injury, and sickle cell crisis. It presents as acute failure of anterior lobe function, the posterior lobe function usually being preserved. Clinical features include severe headache, nausea and vomiting, visual field defects, cranial nerve palsies, and failure of lactation in the parturient. It is treated by management of adrenocortical failure with i.v. fluids and hydrocortisone replacement, and urgent transsphenoidal decompression.

Conclusions

Patients with pituitary disease undergoing pituitary or other surgery can present a host of anaesthetic challenges. Anaesthetists must have a good appreciation of the varied presentation of pituitary disease and their implications for the patient’s perioperative state. Good communication and teamwork between the neurosurgeon, anaesthetist, neuroendocrine service, and the radiologist is fundamental to the successful management of patients with pituitary disease undergoing surgery.

Conflict of interest

None declared.

References


Please see multiple choice questions 16–20.