

# Perioperative management of patients with pituitary tumours

Mary Abraham

## Abstract

Management of pituitary tumours can be very challenging for the anaesthesiologist. These patients require a thorough pre-operative assessment in view of underlying endocrine disturbances, which could cause anatomic and physiological disturbances. This needs to be optimized prior to surgery and the anaesthetic technique planned accordingly. The main intraoperative problems that could be encountered by the anaesthesiologist are airway problems, haemodynamic disturbances and potential for bleeding during surgery. The postoperative concerns are related to the endocrine system and fluid and water balance and this needs to be monitored closely and managed appropriately. The advent of minimally invasive surgery along with neuroimaging has considerably decreased perioperative morbidity and mortality following pituitary surgery. A team approach and close coordination between the endocrinologist, neurosurgeon and anaesthesiologist is imperative for a favourable outcome in patients undergoing pituitary surgery.

**Key words:** Anaesthesia, complications, pituitary tumours

## INTRODUCTION

Pituitary tumours usually occur in adults and represent 10% of all intracranial neoplasms. Surgery for pituitary resection presents unique challenges to the anaesthesiologist, both as an anatomic and functional entity. A thorough understanding of the pathophysiology of the pituitary disease is necessary for the anaesthesiologist to be better equipped to manage these patients in the perioperative period.

Pituitary tumours may be classified according to their size into microadenomas (<10 mm) or macroadenomas (>10 mm) and, according to function, they may be classified as functioning or non-functioning. Functioning pituitary

adenomas produce a single predominant hormone and these are usually anterior pituitary hormones. Since non-functioning tumours are asymptomatic, they usually present later and are more often macroadenomas as early detection is not possible. Macroadenoma, because of its intrasellar growth, can cause hypopituitarism resulting in adrenocortical insufficiency, hypothyroidism, hypogonadism and growth hormone (GH) deficiency. Pituitary adenomas are unlikely to cause diabetes insipidus (DI) in the pre-operative period unless they are infiltrative in nature.

The most common presenting features of patients with pituitary adenomas are headache and visual loss (temporal or bitemporal hemianopia), resulting from compression of the optic chiasma. Pituitary tumours can increase intracranial pressure due to the mass effect *per se*, or by compression of the third ventricle. This could manifest as headache, which may be associated with nausea, vomiting and papilloedema.

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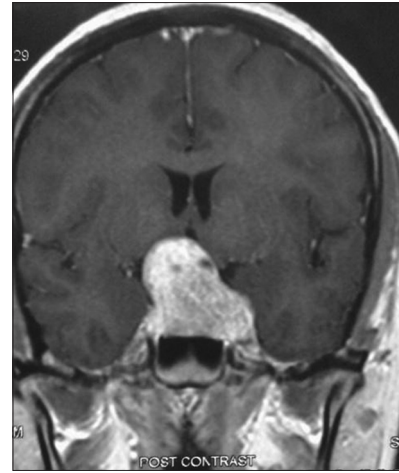
In patients with pituitary apoplexy, which is a rare condition due to acute infarction/haemorrhage of the pituitary gland, the symptoms are more acute in onset and can present in hours or days with neurological, neuro-ophthalmological, humoral and cardiovascular symptoms. This manifests as headache, visual symptoms, meningismus, ophthalmoplegia, decreased the level of consciousness and signs of panhypopituitarism. These patients usually need emergency surgery for a favourable outcome.<sup>[1]</sup>

## PRE-OPERATIVE ASSESSMENT

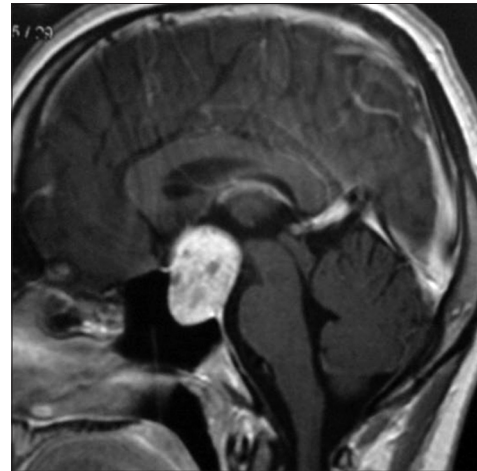
All patients with pituitary adenomas need a thorough endocrinological evaluation in the pre-operative period and follow-up in the post-operative period, especially, in view of the need for hormone replacement therapy. Most often the history, clinical examination and imaging can provide insight regarding the type of pituitary tumour and, hormone profiling serves to confirm the clinical diagnosis. Serum tests include adrenocorticotropic hormone (ACTH), GH (alone or in combination with prolactin), insulin-like growth factor1 (surrogate marker of GH),<sup>[2]</sup> prolactin, follicular stimulating hormone, luteinising hormone, testosterone,  $\alpha$  subunit (alone or in combination) and thyroid stimulating hormone (TSH). A pregnancy test may need to be done in patients with secondary amenorrhoea.

Pre-operative investigations should include complete blood count (CBC) and serum biochemistry. CBC may reveal pre-operative anaemia in elderly patients with pituitary adenoma with low testosterone levels.<sup>[3]</sup> A metabolic panel to detect hyponatraemia, hypercalcaemia and hyperglycaemia should also be done. Visual function evaluation including visual field testing is also done pre-operatively. Standard pre-operative imaging of the sellar and parasellar region typically includes coronal and sagittal magnetic resonance (MR) sequences obtained with or without gadolinium-enhancement [Figures 1 and 2]. Lesions of the sellar and parasellar region are routinely assessed for their size, degree of extension and invasion into surrounding regions, anatomic proximity and association to surrounding structures including, the internal carotid arteries [Figure 3], optic apparatus, degree of suprasellar extension [Figures 4 and 5], and extension into the cavernous sinus. These anatomic relations are significant to both surgeon as well as the anaesthesiologist so that the intraoperative strategy can be planned.

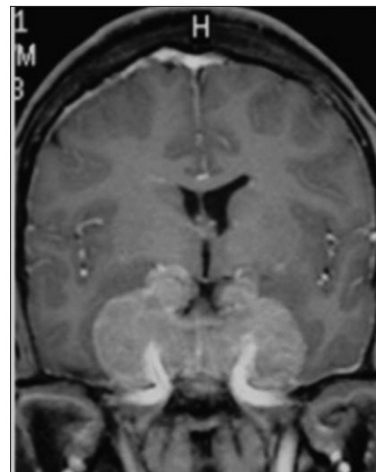
Among the hyperfunctioning pituitary tumours, prolactinomas are most common and constitute approximately 30% of all clinically diagnosed pituitary tumours. Unlike acromegaly and Cushing's disease, anaesthetic management of hyperprolactinomas is less problematic as they are related only to the local mass



**Figure 1:** Magnetic resonance imaging (coronal view) depicting pituitary adenoma



**Figure 2:** Magnetic resonance imaging (sagittal view) depicting pituitary adenoma



**Figure 3:** Large pituitary adenoma encasing both internal carotid arteries

effect of the tumour. More than 90% of these patients respond to medical management. The other clinical

secretory pituitary adenomas that are of relevance to the anaesthesiologist, are GH, ACTH and TSH secreting tumours [Table 1].

## ACROMEGALY

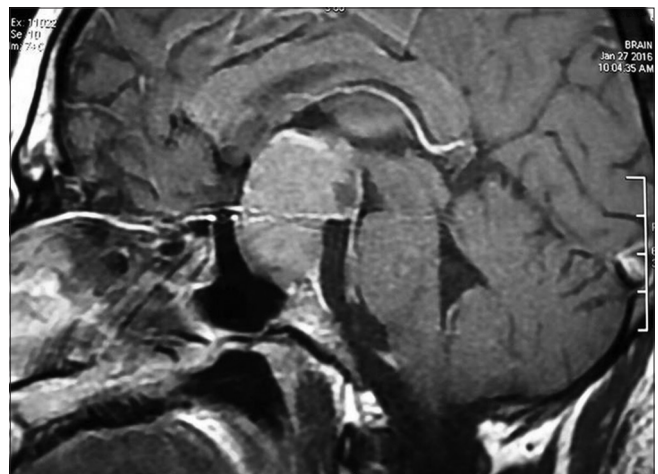
Acromegaly is due to hypersecretion of GH, and its clinical manifestations are primarily due to its physical characteristics and its systemic effects. The physical manifestations, such as prognathism and malocclusion of teeth, are because of coarsening of facial features and bony proliferation and are pathognomonic of acromegaly. There can be thickening of the pharyngeal and laryngeal tissues, hypertrophy of the peri-epiglottic region, calcinosis of the larynx leading to narrowing of the glottic opening and even injury to the recurrent laryngeal nerve. A history of hoarseness of voice and obstructive sleep apnoea (OSA) should alert the anaesthesiologist of possible laryngeal involvement and an ENT referral along with indirect laryngoscopy, and X-ray of the soft tissues of the neck might be indicated. OSA may be present in 70% of acromegalic patients.<sup>[4,5]</sup> In fact, after cardiovascular disease, respiratory disease is the most common cause of sudden death in untreated acromegalic patients.<sup>[2]</sup> While symptoms pertaining

to vocal cord involvement usually resolve soon after surgery, disordered nocturnal breathing may persist even after excision of the pituitary tumour.<sup>[6,7]</sup>

The systemic manifestations of acromegaly include cardiovascular disease, diabetes mellitus and adrenocorticotrophic hypersecretion of which, cardiovascular disease is a major factor contributing to morbidity and mortality, especially in untreated acromegalic patients.<sup>[8]</sup> Hypertension is present in 40% of patients leading to left ventricular hypertrophy [LVH]), although LVH may be present even in normotensive acromegalics. An echocardiography is mandatory in all acromegalic patients.<sup>[9]</sup> Acromegalic cardiomyopathy is characterised by diastolic dysfunction and a poorly compliant left ventricle, with a need for higher ventricular filling pressures.<sup>[10]</sup> It is due to interstitial myocardial fibrosis and may not return to normal after treatment. Right ventricular dysfunction secondary to pulmonary hypertension due to long-standing OSA may also be present.<sup>[11]</sup> The other cardiac manifestations include myocardial ischaemia due to small vessel disease,<sup>[12]</sup>



**Figure 4:** Magnetic resonance imaging (coronal view) depicting pituitary adenoma with suprasellar extension



**Figure 5:** Magnetic resonance imaging (sagittal view) depicting pituitary adenoma with suprasellar extension

**Table 1: Types of secretory pituitary adenomas and their medical management**

Type and incidence	Drug	Action
Prolactinomas - 35%	Dopamine agonists Bromocriptine, cabergoline	Resolves hyperprolactinemia, reduces tumour size, restores reproductive function
GH secreting tumours - 20%	Somatostatin analogues Octreotide, lanreotide GH receptor antagonist Pegvisomant	Inhibits GH production and somatotroph proliferation Reduces production of IGF-1. No reduction in tumour size
ACTH secreting tumours - 7%	Ketoconazole, metyropone	Halts steroidogenesis at the adrenal gland. Does not reduce tumour size or restore normal pituitary function
TSH secreting tumours - <3%	Somatostatin analogue Octreotide	Can suppress TSH secretion. May reduce tumour size

GH=Growth hormone, TSH=Thyroid stimulating hormone, IGF-1=Insulin-like growth factor-1, ACTH=Adrenocorticotrophic hormone

mitral and aortic valve disease, conduction disturbances and electrocardiogram changes.<sup>[13]</sup> The latter two may occur in more than 40% of acromegalic patients. These patients are prone to supraventricular and ventricular arrhythmias, especially during exercise or stress, and this should be kept in mind in the intraoperative period.<sup>[14]</sup>

## CUSHING'S DISEASE

Systemic hypertension, which is present in a majority of these patients, is due to the increase in endogenous corticosteroids resulting in an increase in cardiac output and hepatic production of angiotensinogen. The latter activates the renin-angiotensin system, which causes an increase in the circulating plasma volume. OSA may also be present in these patients although the incidence is lesser than in acromegalic patients. In addition, glucose intolerance may be present, and diabetes mellitus occurs in one-third of these patients. Osteoporosis is present in nearly 40% of patients with Cushing's disease and, pathological fractures are not uncommon. Therefore, care should be taken while positioning these patients. The other problems in these patients include obesity-related problems of airway compromise, gastro-oesophageal reflux, increased fragility of the skin and immunosuppression with increased risk of wound infection.

## MEDICAL MANAGEMENT OF PITUITARY TUMOURS

The treatment goals for secretory adenomas are 3-fold:

- Suppression of hormone secretion
- Decrease tumour size
- Restore normal pituitary function.

These are summarized in Table 1.

## SURGICAL MANAGEMENT OF PITUITARY TUMOURS

The three surgical approaches for pituitary resection include the following:

- Transcranial approach
- Microscopic (transseptal - transsphenoidal approach)
- Endoscopic (transnasal - transsphenoidal approach).

Microscopic transsphenoidal resection of pituitary adenomas using a sub-labial transseptal approach, was the gold standard for pituitary surgery as it was associated with lesser morbidity and mortality than the transcranial approach. However since the late 1990s, after Jho popularised the use of endoscopic surgery, currently the endonasal approach has been found to be even more advantageous than the sub-labial transseptal approach.<sup>[15]</sup> It not only offers a panoramic view of the surgical site, but also is associated with fewer cosmetic,

dental and nasal complications as well as a shorter hospital stay. Moreover, the incidence of DI is also less with this approach.<sup>[16]</sup> The incidence of major morbidities such as intracranial haemorrhage, stroke, meningitis and visual loss is also very low with this technique. One study found that although the remission rates were better with the endonasal route as compared to traditional microsurgery, the incidence of cerebrospinal fluid (CSF) leak was higher with the former approach.<sup>[17]</sup> This is controversial, as a more recent meta-analysis has shown no difference in the incidence of CSF leak, visual complications, meningitis, hypopituitarism, DI or cranial nerve injury with the endonasal approach, although the risk of vascular complications was higher.<sup>[18]</sup>

Computer-assisted navigation and guidance has further improved this technique. MR images (MRIs) with fiducial markers used to identify key anatomic features are obtained before surgery. Intraoperative co-registration of the fiducial markers with the MRI aids in directing the angle of approach and ensuring thorough resection of the tumour during surgery. Intraoperative MRI may be useful in assessing the extent of surgical resection and minimising the risk of tumour remnants.<sup>[19]</sup> Advances in imaging assisted transsphenoidal surgery has been found to improve surgical outcomes with higher remission rates.<sup>[20]</sup> However, these are only tools and there is no replacement for a thorough knowledge of the underlying anatomy and surgical expertise for a good outcome.

## INTRAOPERATIVE MANAGEMENT

### Airway management

Airway management in patients with acromegaly can pose difficulties both during mask ventilation as well as during tracheal intubation. Mask ventilation can be difficult due to thickening of the soft tissues of the nose, mouth, lips and tongue. Both Messick *et al.* and Schmitt *et al.*, in a later study, found that the incidence of difficult intubation in these patients to be 13% which is higher than the normal population.<sup>[21,22]</sup> It has also been found that patients who were initially assessed to be Mallampatti class 1 and 2 had actually a difficult airway.<sup>[22,23]</sup> Thus, a reassuring pre-operative airway examination could be misleading and the anaesthesiologists should be prepared to manage a difficult airway in these patients. Although earlier authors had advocated tracheostomy, nowadays it is not considered necessary. However, various airway devices to aid intubation should be readily available. Use of intubating laryngeal mask airway has met with limited success for unparalysed acromegalic patients because of upper airway abnormalities, especially, a large tongue.<sup>[24]</sup> Similarly, flexible fiberoptic intubation also may be difficult in these patients.<sup>[25]</sup> Awake intubation could thus be a safe option in patients with anticipated

difficult airway. Tracheal intubation in patients with Cushing's disease should also be treated with caution because of obesity and gastro-oesophageal reflux. The endotracheal tube should be fixed securely to the left side of the mouth, for facilitating endoscopic surgery from the right side of the patient. After intubation, a pharyngeal pack is inserted to prevent blood and debris entering the stomach as that could make the patient prone to nausea, vomiting and aspiration in the post-operative period.

### Monitoring

Besides routine monitoring, intraarterial pressure monitoring is indicated for several reasons during transphenoidal surgery, which includes pre-existing cardiovascular disease, optimal blood pressure management including, permissive hypotension during dissection and also in view of the potential vascular complications that could occur during tumour resection considering the proximity of internal carotid artery (ICA) to the pituitary. Caution must be exercised for arterial cannulation in acromegalic patients with carpal tunnel syndrome as they are 'radial artery dominant' and, alternate sites of arterial cannulation may need to be used. Because of the potential although rare risk of venous air embolism, a central venous catheter may be necessary although in practice it is rarely used. Routine monitoring should also include urine output measurement especially, in view of the likelihood of DI in the post-operative period. As permissive hypercapnia may be required in patients with suprasellar extension to cause descent of the tumour, end tidal CO<sub>2</sub> monitoring may need to be closely watched. The role of visual evoked potential monitoring (VEP) is debatable although some authors have reported post-operative visual field improvement with intraoperative VEP monitoring.<sup>[26]</sup> But given the lack of strong evidence and the high incidence of 'false positive rate' because of the exquisite sensitivity of VEP to anaesthetics and technical difficulties in monitoring it in the operating room, it is not advocated during transphenoidal surgery.

### Anaesthetic management

The goals of anaesthetic management for minimally invasive surgery of pituitary adenomas are airway management, haemodynamic control, facilitation of surgical exposure and early emergence to facilitate a neurological examination.

Perioperative steroid administration should be guided by 8 h cortisol and short ACTH 1–24 (synacthen) test. If test results are normal (cortisol >550 nmol/L), no perioperative glucocorticoid is required. If the test is abnormal, the patient should be given supraphysiological glucocorticoid cover for 48 h post-operatively (e.g., hydrocortisone, 50 mg every 8 h on day 0, 25 mg every 8 h on day 1, and 25 mg at 8 h on day 2). All patients with Cushing's disease require glucocorticoid cover.<sup>[27]</sup>

The operating room environment for pituitary surgery, especially if it is fully endoscopic, would mean that the anaesthesiologist has poor access to the patient's face and airway. The head of the patient may be fixed on a Mayfield clamp if frameless stereotaxy is being used and also for good surgical access. Long extension lines, both arterial and venous, and special care to ensure that the airway is secure is absolutely necessary to provide safe 'long distance' anaesthesia.

The endoscopic endonasal approach to the pituitary gland involves intranasal dissection and since these structures are vascular, infiltration with local anaesthetic combined with a vasoconstrictor along with maintaining blood pressure in the low normal range, 'permissive hypotension', can facilitate a clear surgical field. This can be especially challenging as endonasal surgery, especially after infiltration with a vasoconstrictor, evokes a strong sympathetic response. Thus, a combination of deep anaesthesia along with antihypertensive medications is usually necessary to maintain the blood pressure in the optimum range. Pasternak *et al.* found significant hypertensive responses to nasal injection and at the time of emergence in patients undergoing transphenoidal surgery irrespective of the type of endocrinopathy (acromegaly or Cushing's disease). They were not able to find a variable that could predict which patient is likely to experience this hypertensive response.<sup>[28]</sup> Epinephrine infiltration during pituitary surgery can be hazardous and intraoperative hypertensive crisis followed by post-operative myocardial infarction has been reported.<sup>[29]</sup> Various anaesthetic agents such as propofol and remifentanyl infusion and inhalational agents such as sevoflurane have been used with success although, addition of remifentanyl to the anaesthetic allows for faster recovery times as compared to volatile agents alone.<sup>[30]</sup> Ali *et al.* used studied the effects of bispectral guided administration of isoflurane, sevoflurane and propofol on haemodynamics and recovery characteristics in patients undergoing transphenoidal resection of pituitary tumours. These authors found better recovery profile in sevoflurane and propofol groups and a better cognition in patients receiving propofol and they concluded that propofol plus nitrous oxide anaesthesia could be the technique of choice in these patients.<sup>[31]</sup>

In patients with suprasellar extension, the anaesthesiologist may be requested to assist descent of the suprasellar part of the tumour into the sella to facilitate resection. Several techniques may be employed to transiently raise the ICP and lower the tumour which include, Valsalva manoeuvre, high normocapnoea to a PaCO<sub>2</sub> in the range of 40–45 mmHg and intrathecal instillation of air or normal saline.<sup>[32]</sup> Korula *et al.* found controlled hypercapnia up to a limit of 60 mmHg to be a simple and effective method of lowering the suprasellar

part of the tumour into the sella, without any deleterious effects.<sup>[33]</sup> Lumbar subarachnoid infusion of saline along with gentle traction has also been described to bring the suprasellar portion of the tumour progressively into the line of vision.<sup>[34]</sup> However, this is done with caution, preferably monitoring the ICP and under strict asepsis. The same lumbar drain may be left *in situ* for subsequent CSF drainage if a CSF leak has occurred during surgery.

Blood loss during surgery is usually minimal. However, there is a potential for intravascular complications and the operating team including, the anaesthesiologists should be vigilant and fully prepared to handle such emergencies. Injury to the ICA can rarely occur, especially during aggressive dissection of macroadenomas that extends into the cavernous sinus or encase the ICA [Figure 3], or during reoperation when there are anatomic alterations of the region. If there is sudden and profuse bleeding intraoperatively suggestive of iatrogenic carotid artery injury, haemorrhage must be controlled with tamponade, immediate cerebral angiographic study is indicated to determine the source of bleeding and steps must be taken to control the situation. The anaesthesiologist must assist the neurosurgeon in managing such emergencies by supportive management with rapid fluids and blood transfusion and maintain haemodynamic stability.

### Emergence from anaesthesia

Valsalva manoeuvre up to intrathoracic pressures of 30–40 mmHg may be needed before closure so that the surgeon can check for adequate haemostasis and CSF leaks. At the end of surgery, the anaesthesiologist has to ensure that there is smooth emergence from anaesthesia to prevent formation of haematoma in the surgical bed as well as to prevent dislodgement of the fat graft. The latter could predispose the patient to complications such as post-operative meningitis and CSF leak. This entails prevention of hypertension as well as coughing or 'bucking' on the endotracheal tube. Upper airway obstruction that is likely to occur in these patients could also lead to a stormy emergence and should be prevented by use of airway adjuncts.

## POST-OPERATIVE MANAGEMENT

### Airway management

Maintaining the airway in post-operative period is of utmost importance as it could get compromised because of pre-existing acromegalic features, nasal packing as well as a likelihood of aspiration of blood and debris from the stomach. Acromegalic patients with OSA should be closely monitored as there is a high risk of perioperative airway complications and care should be taken while administering sedative drugs.

### Post-operative pain management

Flynn and Nemergut in a large series observed that the post-operative analgesic requirement is very low in patients who had undergone transsphenoidal surgery.<sup>[35]</sup> Since pituitary gland has the highest concentration of endogenous opioids, it is possible that surgical manipulation releases endogenous opioids resulting in low requirements of exogenous opioids. Non-opioid analgesics like intravenous paracetamol, has an opioid sparing effect and is useful in controlling post-operative pain. Moreover, opioids should be used with care in patients with history of OSA.

### Neurological function

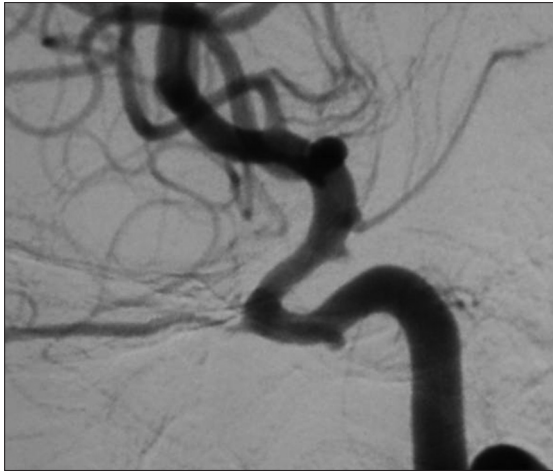
Early neurological examination and assessment of visual function should be done in the immediate post-operative period. If acute haematoma occurs, there could be onset of sudden blindness and ophthalmoplegia along with acute deterioration of consciousness and hypotension. An urgent computed tomography scan is indicated in such scenario.

### Management of endocrine function

All patients need to be screened for hypopituitarism to ascertain the need for post-operative hormone replacement therapy. It is important to review the extent of surgery as well as the pathology report to determine the need and type of hormone replacement. Most patients with pre-operative normal pituitary function will remain so post-operatively. Of the patients who have pre-operative hypopituitarism, 27% will regain normal function after pituitary surgery. Early post-operative assessment depends on daily clinical assessment of the patient and 8 h plasma cortisol levels. This should reduce the use of unnecessary glucocorticoids, while ensuring the safety of patients is not compromised.<sup>[27]</sup>

## POST-OPERATIVE COMPLICATIONS

These can broadly be classified as anatomic or endocrinological. Gondim *et al.* in a retrospective review of 301 patients who underwent endoscopic pituitary resection found the incidence of anatomic complications to be 8.97% which also included intrasellar/suprasellar or pontine haematoma.<sup>[36]</sup> Figure 6 depicts a pseudoaneurysm of the ICA and Figure 7 depicts a pontine haematoma following endoscopic resection of pituitary. Anatomic complications can also include cranial nerve injury and post-operative CSF leak. If a CSF leak is suspected intraoperatively, a lumbar intrathecal catheter is inserted just before extubation of the patient if it had not been inserted at the beginning of surgery. However, sometimes, the neurosurgeons would need to resort to operative repacking of the defect with an autologous fat graft. Continuous lumbar CSF drainage usually promotes resolution of the leak post-operatively.



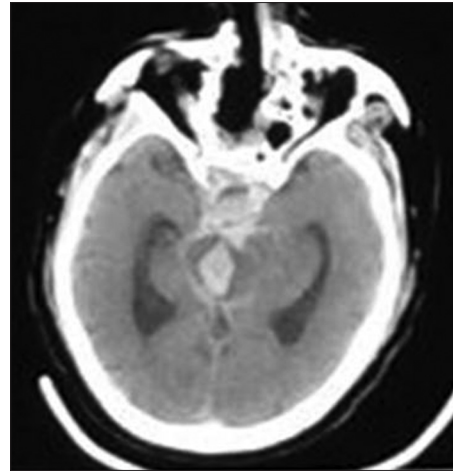
**Figure 6:** Digital subtraction angiography depicting pseudoaneurysm of internal carotid artery following endoscopic endonasal pituitary surgery leading to severe bleeding during surgery

The incidence of endocrinological complications was found to be 17.9%.<sup>[36]</sup> Both DI and syndrome of inappropriate anti-diuretic hormone secretion (SIADH) can occur. The incidence of DI is comparatively higher after transcranial resection as compared to transsphenoidal surgery. It can be either transient or permanent. The incidence of permanent DI after transsphenoidal surgery in one study has been found to be 2% and that of transient DI 16.6%.<sup>[37-39]</sup> It usually manifests in 24 h after surgery as polyuria, thirst and polydipsia and a strict watch on intake, output and serum sodium levels is necessary. Fluid losses are replaced initially with isotonic saline and later with hypotonic fluids depending on serum sodium levels. Since transient DI is encountered most commonly (>95% of times), a single dose of desmopressin (DDAVP) is usually sufficient. However, care should be taken to ensure that 'overshoot' hyponatraemia and water retention does not occur. In a series of over 800 patients who underwent transsphenoidal surgery, Nemergut found that 12.4% of patients required to be administered DDAVP in the post-operative period.<sup>[37]</sup>

The incidence of SIADH varies between 9% and 25% following pituitary surgery.<sup>[38]</sup> This manifests as hyponatraemia associated with either euvoalaemia or mild hypervolaemia, low serum osmolarity and high urine osmolarity. Treatment is usually fluid restriction, unless symptomatic hyponatraemia occurs when hypertonic saline needs to be administered. The latter needs to be given with caution to avoid the rare but potentially serious complication of central pontine myelinolysis.

## CONCLUSION

Perioperative management of pituitary surgery is very challenging and requires a team approach



**Figure 7:** Magnetic resonance imaging showing a pontine haematoma following endoscopic endonasal pituitary surgery

by neurosurgeons, neuroanaesthesiologists and endocrinologist. The advent of endonasal transsphenoidal pituitary surgery has improved the outcome of pituitary surgery with fewer complications, more complete resections and shorter hospital stay. Some of the challenges that the anaesthesiologist face are related to the endocrine system and perioperative hormone therapy, airway management, intraoperative haemodynamic stability, and post-operative disorders of fluid and sodium balance.

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## Conflicts of interest

There are no conflicts of interest.

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