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Acromegaly and Gigantism

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Introduction

- *Acromegaly ('acron' = extremity, 'megale' = great)* is a rare clinical syndrome with only 3 to 4 cases per million seen annually. The paediatric form is called gigantism and is mainly due to mutations of *aryl hydrocarbon receptor-interacting proteins* (AIP) or abnormalities in the gene GPR101 resulting in pituitary adenomas.[1] *Gigantism* is extremely rare[2] but the diagnosis is usually easier than in acromegaly.[3] Other causes of gigantism may be MEN1, Carney complex and McCune-Albright syndrome.[3] These children usually present 2 standard deviations taller than their peers. Pituitary adenomas in children also tend to be locally aggressive and often break through the sella turcica. The other manifestations are very similar to acromegaly and will be discussed below.[3]
- Acromegaly is a chronic progressive multisystem disease seen in adults and is mainly caused by anterior pituitary tumours (macroadenomas, i.e. a tumour greater than 1 cm in size) that secretes excessive growth hormone (GH) from the pars distalis.[4] It is a disease of middle age (4th to 6th decade.)[5] The onset is insidious and is usually advanced before the diagnosis is made.[3] The average time for diagnosis is 6–8–13,4 years.[3,6]

Pathogenesis

a. Anatomy

- The pituitary is situated in the sella turcica and surgery may damage the following adjacent structures: Hypothalamus, 3rd ventricle, cranial nerves III, IV, V, VI, cavernous sinus and most importantly internal carotid arteries. Damaging the carotid artery or cavernous sinus intraoperatively may cause life-threatening haemorrhage.[4]
- A common complaint which makes the patient seek medical help is often visual field temporal and bitemporal hemianopia defects[5] due to pressure on the optic chiasma. Other cranial nerve defects may also occur. Raised intracranial pressure may also cause headaches and papilloedema.
- An enlarged sella turcica on skull X-ray is pathognomonic of a pituitary adenoma. Treatment is surgical excision via transsphenoidal access.
- If the tumour extends beyond the sella turcica, surgery and radiation may no longer be feasible[4] and medical treatment may then be preferred using somatostatin analogues such as ocreotide and lanreotide. These drugs however, may cause severe vomiting and diarrhoea. Bromocriptine, a dopamine agonist, may also be used to decrease growth hormone levels but severe postural hypotension may preclude its use.[7]

b. Pathophysiology

- Growth hormone releasing factor (GHRF) is produced by the hypothalamus which stimulates somatotrophs in the anterior pituitary gland to produce a 191 amino acid, GH or somatotropin. Rarely, the cause of acromegaly is from a tumour in the hypothalamus or by other non-endocrine tumours (see section below on the laboratory diagnosis of acromegaly).[3]
- GH is a stress or anabolic hormone that increases glucose and fatty acids. It appears to have 2 main functions:
    - It increases growth and cell production.
    - It also stimulates the production of **Insulin-like growth factor 1** (**IGF-1**) or **somatomedin C** in the liver. IGF-1 has a similar molecular structure to insulin. In children it promotes growth and in adults it is anabolic. There are IGF-1 receptors in almost every organ in the body except the brain (see Table 1).[4]
- GH levels fluctuate following a circadian rhythm and for this reason constant IGF-1 levels are used to determine whether the patient has acromegaly or gigantism. However, it is important to note that IGF-1 levels normally range from 10–1000 ng/ml and so interpretation may be difficult. Also IGF-1 may be normal in 5–10% of patients with acromegaly.[8] In a rare subgroup of patients IGF-1 is increased due to the production of IGF-binding protein which prevents the breakdown of IGF-1.[3]

Table 1: Organs targeted by an excess of GH and IGF-1:(2)

Bone	• Anabolic effects [4] cause bone mineralisation.[2] • This leads to an increase in bone production and turnover, increasing urinary sodium, hyperphosphataemia and renal stones.[6] • In children the epiphyseal growth plates are still open and therefore the long bones elongate causing *gigantism*. • In adults the bones hypertrophy, causing *acromegaly*. • Facial features become characteristically coarse with macrognathia. • Increased length of the mandible may make upper airway management difficult, i.e prognathism causes a thyromental distance > 9. • The hands and feet also increase in size.[2] Patients may report an increased shoe size, but large "spade-like" hands are commonly seen.[2]
Cartilage	• Chondrocytes in cartilage proliferate. • Hypertrophic arthritic joints may occur.[3] • Patients may complain of back pain with or without kyphosis.[3]
Muscle	• Anabolic effects[4] cause sarcomere hyperplasia and protein synthesis leads to hypertrophied muscle. • Skeletal muscle weakness may be prominent and complaints of fatigue are common. • There is an increased incidence: ▫ Hernias ▫ Colonic polyps ▫ Cancer of oeophagus, stomach and colon.[6]
Soft tissue	*Peripheral nerves* • Carpal tunnel syndrome commonly occurs (64–80% of acromegalic patients have abnormal nerve conduction studies which may be due to oedema and demyelination).[2] A symptomatic patient could have compromised blood flow through the ulnar artery, and insertion of an arterial line into the radial artery may result in no blood supply to the hand.[9] • Also, even in the absence of symptoms of carpal tunnel compression, approximately a third have inadequate blood flow through ulnar artery in one or both hands. • Peripheral neuropathies are common elsewhere and reflect trapped nerves from skeletal, soft tissue and connective tissue overgrowth.[10] Myopathy of intercostal nerves may further compromise respiratory function already decreased by kyphoscoliosis.[2] *Dermis* • The skin becomes thick and oily due to excessive sebum production from cutaneous glands.[6] *Sweat glands* • Perioperative hidrosis or sweating may be excessive causing adhesive dressings and monitoring stickers to become detached. This is also due to stimulation of cutaneous glands.[6]
Adipose	• There is an increased lipolysis leading to increased free fatty acid (FFA) levels.[4]
Immune system	• Hormones and neuropeptides are known to be potent immunomodulators. This may lead to colon polyposis and blood dyscrasias.[11, 12]
Visceromegaly	*Cardiac* • Dilated cardiomyopathy occurs in a subset of patients. Myofibrillosis and interfascicular fibrosis can be seen on histology.[8] • There is an increased incidence of: ▫ Eccentric left ventricular hypertrophy (LVH) due to sarcomere hypertrophy or due to increased afterload from hypertension that occurs in 50% of patients. LVH can occur in normotensive patients. ▫ Ischemic heart disease is prevalent as there is increased oxygen demand from hypertrophied tissues as well as a resultant diastolic dysfunction. ▫ Arrhythmias and heart blocks can occur as the heart enlarges and stretches the conduction system.[13, 14] *Lung* • Pneumomegaly occurs to due to an increased number of alveoli. Ventilation/Perfusion (V/Q) mismatch may be enhanced.[2] • In 25–75% of patients, mucosal thickening of the upper airways and bronchi may be seen.[2] • An enlarged thyroid gland may cause tracheal compression in 25% of patients.[15] *Kidney* • Increased size is not significant.[6] *Hepatic* • Increased liver size is not significant. • An increase in hepatic gluconeogenesis does occur due to a decrease in hepatic glucose uptake. • As previously mentioned, this results in an increase of IGF-1. IGF-1 may also be produced in other target cells. • IGF-1 is a potent stimulator of cell growth and all tissues proliferate.[6] *Body weight* • Weight increases as lean body mass increases.[6]
Metabolic	• GH impairs glucose utilisation and promotes lipolysis, increases FFA levels and causes a cellular sensitivity to insulin.[3] • Glucose intolerance or frank diabetes requiring insulin reflects the effects of GH on carbohydrate metabolism and occurs in approximately 28% of patients.[16]

The above table deliberately did not include concerns regarding the airway. Difficult intubations in acromegaly are known to be a major cause of morbidity and mortality. Table 2 details problems in these patients.[17,18]

Table 2: Airway considerations in Acromegaly

Mandible	• Macrognathia
Soft tissue overgrowth	• Macroglossia, thickened lips and an enlarged epiglottis and tonsils impede visualisation of the vocal cords. • Polyploid masses may develop in pharyngeal tissue, making the airway susceptible to obstruction. Obstructive Sleep Apnoea ***(OSA)*** occurs in 60–70% with snoring and daytime somnolence. The OSA is usually the obstructive type but centrally mediated depression of respiratory drive may occur due to narrowing of the upper airways which induces reflex inhibition of the respiratory centre.[19,20] • Thickening of epiglottis and aryepiglottic folds may also occur.
Connective tissue	• Recurrent laryngeal nerve paralysis is caused by stretching of tissues as the cartilaginous structures in the neck expand. • This results in abnormal movement of the vocal cords with voice alteration and hoarseness. • Impaired mobility of the cricoarytenoid joints may also occur.[2]
Vocal cords	• Chondrocalcinosis of larynx results in vocal cord thickening and stricture formation.[2] • Cricoarytenoid joint involvement causes impaired movement of the vocal cords and therefor voice alterations. ***If you suspect vocal cord thickening or laryngeal pathology (grades 3 and 4 mentioned below), consider awake intubation with a bronchoscope.*** • Subglottic dimensions can be decreased. • Stridor and dyspnoea may suggest upper airway involvement. • Grading system: a) Grade 1: no involvement b) Grade 2: nasal and laryngeal hypertrophy only c) Grade 3: glottis involvement d) grade 4: presence of grade 2 and 3[6]
Rhinorrhoea	• Postoperative complication.

Laboratory investigations for diagnosis

- Glucose tolerance testing may show failure of plasma GH concentration to decrease 1 to 2 hours after ingestion of 75 to 100 g of glucose. This is presumptive evidence of acromegaly.[3]
- GH levels > 3 ng/ml are very suggestive of acromegaly. Pituitary tumours are found in 95% of patients with a raised GH. The other 5% have GH-secreting tumours in:
  a. Intermesenteric islet cells
  b. Non-Hodgkin's lymphomas
  c. Residual ectopic pituitary remnants in surrounding structures such as nasal cavity and sphenoid sinus.
  d. Genetic conditions: MEN 1, McCune-Albright syndrome, Carney complex.[4]
- Peripheral endocrine tumours arising from pancreas and thymus.[5]
- Therefore other endocrine abnormalities should be excluded (thyroid, pancreas, etc.)
- GH fluctuates according to a diurnal circadian rhythm and therefore IGF-1 which is constant should also be measured.
- A skull X-ray, CT or MRI to see enlargement of sella turcica which is characteristic of an anterior pituitary adenoma.

Preoperative evaluation

Once the diagnosis of acromegaly has been made, a patient coming to theatre needs preoperative multidisciplinary consultations, which should include endocrinology, cardiology and otorhinolaryngology.

a. Endocrinology and/or Physician

- Laboratory testing should include:
  ° Glucose tolerance testing as 25% are diabetic and may have perioperative glucose intolerance.
  ° Urea and electrolytes as renal impairment may be present from hypertension.
  ° Blood gas analysis[6]

b. Cardiology

- In acromegalic patients, cardiac pathology is the most common cause of morbidity and mortality.[2]
- A routine ECG will show dysrhythmias and chamber enlargement.
- Stress testing to exclude ischaemic heart disease is necessary in some patients.[2]
- ECHO if patient is symptomatic or has murmurs. Look for LV size and pulmonary pressures.[4] Also diastolic dysfunction and LV ejection fraction may not increase with stress,[2] especially if the patient has poor exercise tolerance from muscle weakness.
- Hypertension occurs in 40%.
- Incompetent heart valves may also occur.
- Cardiomyopathy (dilated) may be present and diastolic dysfunction may be an early sign.[6,13]
- Chest X-ray, if cardio-respiratory symptoms are present.

c. Otorhinolaryngologist

- ENT assessment with indirect laryngoscopy is essential to quantitate the degree of vocal cord dysfunction. This is especially relevant in patients with stridor and hoarseness.
- Obstructive sleep apnoea (OSA) may be a major concern and affects 60–70% of these patients.[19]

Intraoperative management

a. General principles:

- Patient size makes positioning difficult and a long table may be required.[2]
- Nerve compression is a problem and padding of vulnerable areas, such as median nerve, ulnar nerve at wrist and anterior peroneal nerve behind the knee is imperative.[6]
- Excessive peripheral soft tissue deposition may make venous cannulation difficult.[4]
- Arterial cannulation should not be withheld as it has been found to be safe if the artery is not trapped between carpel bones and the carpel ligament.[2]
- Due to the large face, bag-mask ventilation may be difficult.
- Difficult laryngoscopy is three times more common in acromegaly than in other pituitary tumours.[18] Standard airway assessment manoeuvres, such as the modified Mallampati, thyromental distance, mouth opening and upper lip bite test[18] have not been found to be predictive, as they do not assess involvement of the glottis and epiglottis.
- If direct laryngoscopy is attempted, it may be wise to use the large laryngoscope blade as distance between lips and vocal cords will be increased by macrognathia.
- Videolaryngoscopy may be useful if a big tongue and epiglottis impedes the line of vision.
- A smaller endotracheal tube should be used due to possible narrowing of cricothyroid ring and glottis opening.[3] A reinforced tube is a good choice as a preformed tube may be too short.
- Awake bronchoscopic intubation is seldom required, but should be done if grades 3 and 4 are present.[6]
- Elective tracheostomy should be considered if patient has severe respiratory obstruction (rare).
- Nasal turbinate enlargement precludes the passage of nasopharyngeal or nasotracheal intubation. Oral intubation will be necessary for transsphenoidal hypophysectomy.
- Increased tidal volumes may be necessary due to the increased lung size.
- Use nerve simulator to assess neuromuscular blockade as patient may have pre-existing muscle weakness.
- Watch hydration because of hyperhidrosis. Hypovolaemia will not be tolerated in a patient with diastolic dysfunction.[2]
- Skeletal changes may make regional anaesthesia difficult or unreliable.
- If evidence of OSA, extubatiom should be done only if patient is awake and sitting up. Unfortunately, a nasopharyngeal airway cannot be used post hypophysectomy.
- Consider ventilating the patient in ICU if OSA is severe. The neurosurgeon would prefer an awake patient to act as their own cerebral monitor, but this may not always be feasible.

b. Transsphenoidal pituitary surgery

- A large bore peripheral intravenous line is advisable as well as an arterial line.
- Lines may have to be sutured in place, as hyperhidrosis tends to cause the adhesive dressings to loosen.
- Venous air embolism (VAE) is extremely rare and may be due to entraining air through inter-cavernous venous channels, inadequately sealed nasal bones and from the pituitary itself.[21]
- A lumber drain may be inserted after induction and is said to be beneficial for cerebrospinal fluid (CSF) leaks.[22]
- Dexmedetomidine has been used for intra- and postoperative management.[23, 24]

  However, use in this scenario in South Africa is "off-label". Advantages of dexmedetomidine are controlled haemodynamics, improved field of vision for the surgeon and decreased anaesthetic requirements. While it may not facilitate rapid emergence as the context sensitive half-life is 30 minutes, it decreases intra- and postoperative use of opioids [decreased postoperative nausea and vomiting (PONV)[25] and respiratory depression].
- Neuro-navigation is used during endoscopic transsphenoidal hypophysectomy.[26]

Postoperative considerations: [27]

- Early postoperative period:
  - Stroke
  - Other neurological abnormalities: visual loss or other cranial nerve abnormalities
  - OSA
  - CSF leakage/meningitis
  - PONV occurs in 40% of patients. Prophylactic pharmacological management is advised. Dexamethasone may inhibit the adrenopituitary axis.[25]
- Diabetes insipidus is seen in 0.5–25% of patients. It would appear that immediate incidence after endoscopic transsphenoidal approach is less than with the traditional method.[28]
- Syndrome of inappropriate antidiuretic hormone (SIADH) is also seen in 0.5–25% post-transsphenoidal hypophysectomies.
- Panhypopituitarism occurs extremely rarely.

Conclusion

- These patients may have been chronically ill for many years and therefore require careful handling.
- The systemic effects of the disease may be life-threatening and an adequate medical work-up is essential prior to surgery.

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