Acromegaly

Acromegaly is a rare clinical condition resulting from excess growth hormone secretion. It is named after the Greek words 'akron' – extremities and 'megas' – large, to describe the typical physical appearance associated with the condition. This article discusses the causes, clinical manifestations, diagnosis and management of the disease.

Growth hormone physiology

Growth hormone is under the control of the hypothalamic growth hormone-releasing hormone, which stimulates growth hormone synthesis and release. Physiological stimulators of growth hormone secretion include sleep, stress, physical exercise, acute fasting or malnutrition and hypoglycaemia. The stomach orexigenic hormone ghrelin also stimulates growth hormone release. Somatostatin (produced by the pancreas, other peripheral tissues and the brain) inhibits growth hormone-releasing hormone secretion, thereby inhibiting growth hormone production. The inhibitory effects of somatostatin on growth hormone are being exploited in the medical therapy of acromegaly and will be discussed in the treatment section (*Figure 1*).

Prevalence and causes of acromegaly

Acromegaly has an estimated prevalence of 60 per million and an annual incidence of 3–4 cases per million of population. It affects both genders equally and the mean age at diagnosis is 40–45 years (Holdaway and Rajasoorya, 1999). More than 90% of cases result from a benign pituitary growth hormone-secreting adenoma (somatotroph adenoma) (Melmed, 2006).

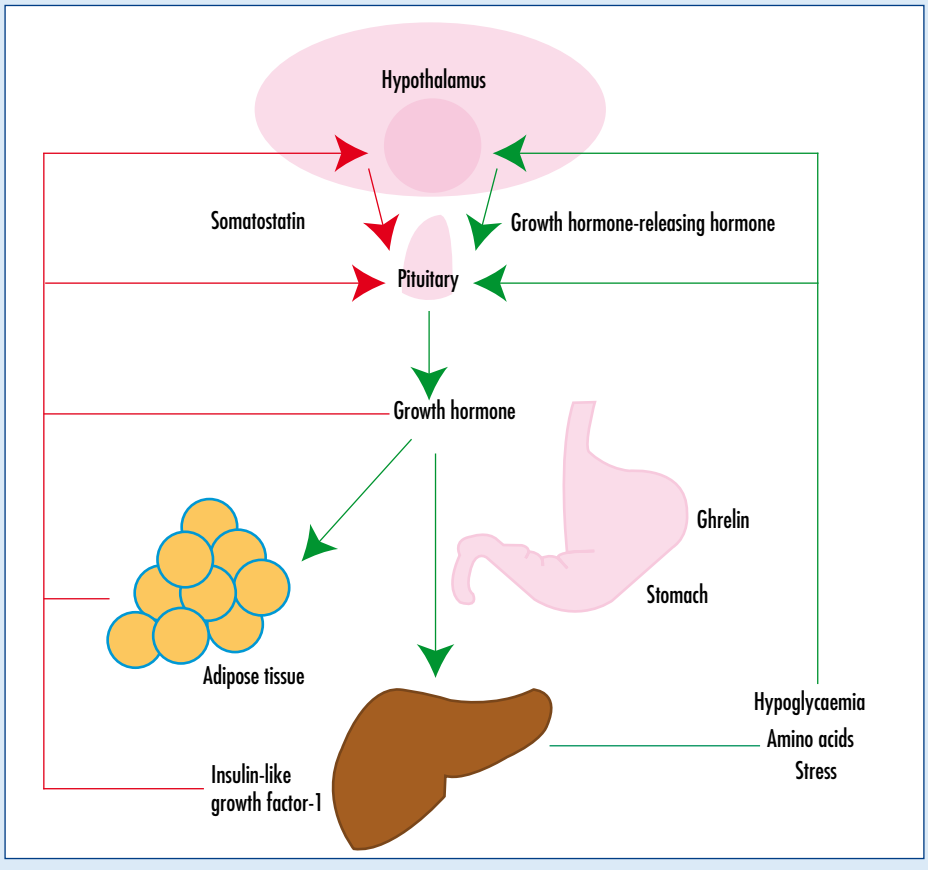
Pituitary carcinomas are extremely rare. Other infrequent causes of acromegaly are growth hormone-releasing hormone-hypersecretion from a hypothalamic tumour, ectopic growth hormone or growth hormone-releasing hormone secretion by neuroendocrine tumours, or ectopic growth hormone-releasing hormone release from small cell lung cancers. Occasionally acromegaly can occur in the context of a genetic syndrome such as familial isolated pituitary adenoma, multiple endocrine neoplasia type 1 syndrome, McCune–Albright syndrome and Carney's syndrome (Holdaway and Rajasoorya, 1999).

Clinical manifestations of acromegaly

The disease is characterized by insidious onset of symptoms with a considerable delay, typically between 6 and 10 years, before the diagnosis is established (Melmed, 2006). Patients commonly complain of non-specific symptoms, such as generalized weakness, musculoskeletal pains and lethargy (Reddy et al, 2010). The symptoms and signs of acromegaly are listed in *Table 1*.

More than 70% of growth hormone-secreting adenomas are large tumours (macroadenoma >1 cm in diameter) and can present with local mass-related symptoms, such as headache, visual field defects (most commonly bitemporal hemianopia) and ophthalmoplegia (Drange et al, 2000). Enlargement of the tumour may result in

Figure 1. Growth hormone physiology. Growth hormone is secreted from the somatotroph cells of the anterior pituitary. Once released into the circulation, growth hormone stimulates the production of insulin-like growth factor 1, which is the primary mediator of the growth-promoting effects of growth hormone. The most abundant source of insulin-like growth factor 1 is the liver, although other tissues contribute to circulating insulin-like growth factor 1. Red arrows and connecting lines signify negative feedback or inhibitory effect while green indicate positive feedback or stimulatory effect.



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deficiency of other pituitary hormones, most commonly gonadotrophins (Drange et al, 2000). Hyperprolactinaemia as a result of prolactin co-secretion from the somatotroph adenoma (Melmed, 2006) or of pituitary stalk compression can contribute to hypogonadism in the context of acromegaly. Other pituitary hormonal deficits may occur as a result of enlargement of the adenoma or as a result of acromegaly treatment.

Table 1. Clinical manifestations of acromegaly

Constitutional	Fatigue
	Generalized weakness
	Lethargy
Local mass effects	Headache (60%)
	Visual field defects or ophthalmoplegia (10%)
Facial features	Coarse acromegaloid facial features
	Enlargement of the nose and lips
	Prominence of the frontal bones and supraorbital ridges
	Prognathism with interdental separation and jaw malocclusion
Dermatological	Skin thickening
	Hyperhidrosis (30%)
	Skin tags
Musculoskeletal	Acral enlargement
	Thickening of the soft tissue of the hands and feet
	Increase in glove, shoe or ring size
	Early large joint and axial degenerative arthropathy (70%)
	Kyphoscoliosis
	Carpal tunnel syndrome (20–50%)
Cardiovascular system	Hypertension (40%)
	Left ventricular hypertrophy
	Cardiomyopathy
	Congestive heart failure (3%)
	Arrhythmias
	Valvular heart disease, most commonly aortic regurgitation (30%) or mitral regurgitation (5%)
Respiratory system	Swelling of nasopharyngeal tissue
	Pneumomegaly
	Obstructive sleep apnoea (50%)
	Central apnoea as a result of direct effects on respiratory centre
Visceral enlargement	Macroglossia
	Nodular, diffuse thyroid enlargement, goitre
	Liver, spleen, prostatic enlargement
Metabolic and endocrine effects	Impaired glucose tolerance or overt diabetes mellitus (19–56%)
	Hypertriglyceridaemia
	Hyperphosphataemia
	Hypercalciuria
	Hyperprolactinaemia (30%)
	Hypogonadism (53%)
	Other pituitary hormonal deficits

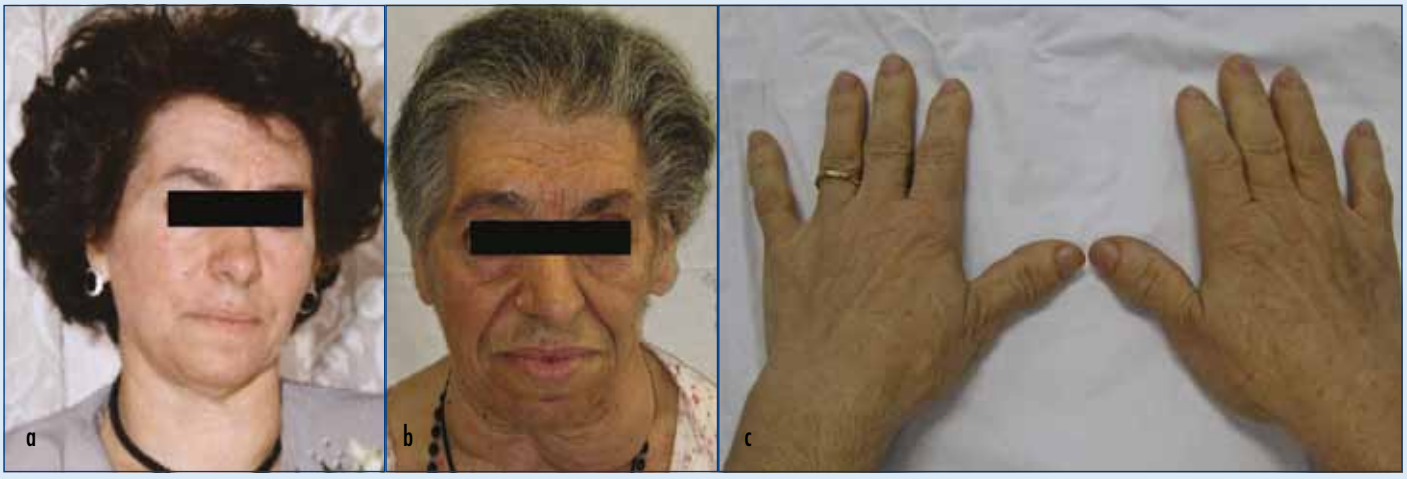
The excess circulating growth hormone and insulin-like growth factor 1 (IGF-1) stimulate tissue growth affecting the skin, connective tissue, cartilage, bone and viscera. The somatic effects arising from the growth-promoting effects of growth hormone or IGF-1 result in the distinctive physical appearance of the disease (*Table 1* and *Figure 2*). Excess growth hormone occurring in children and young adults, before the closure of the epiphyseal plates, accelerates linear growth and results in gigantism (Melmed, 2006).

Moreover the excess circulating growth hormone or IGF-1 induces metabolic effects such as insulin antagonism, lipolysis and electrolytic disturbances. Of patients with acromegaly 19–56% develop diabetes mellitus (Reddy et al, 2010).

Diagnosis

Diagnosis of acromegaly is based on biochemical confirmation of growth hormone excess. Growth hormone secretion is pulsatile and diurnal (Iranmanesh et al, 1994) and factors such as the timing of the sample, patient activity or previous food intake need to be accounted for when interpreting growth hormone results. Patients with acromegaly have increased growth hormone levels and, in contrast to healthy subjects, exhibit loss of diurnal variation of serum growth hormone and display little or no response to physiological regulators of growth hormone secretion. Owing to the pulsatile nature of growth hormone a single growth hormone measurement is of little use in

Figure 2. Phenotypic features of acromegaly. a. Pre-diagnosis, patient aged 40 years. A moderate-sized goitre of the thyroid gland can be seen. b. At diagnosis, aged 60 years. Coarse acromegaloid facial features with enlargement of the nose and jaw, thickening of the lips, presence of skin tags over the neck, and significant enlargement of the patient's left-sided thyroid goitre compared to (a) are seen. c. View of the patient's hands, aged 62 years (at diagnosis).



either or confirming the diagnosis of acromegaly or monitoring disease activity. Serum growth hormone is elevated in patients with uncontrolled diabetes mellitus, liver disease and malnutrition and this needs to be considered during interpretation of results.

A simple blood test for growth hormone and IGF-1 in general practice is often sufficient to evaluate patients with suspected acromegaly. Random growth hormone levels below 0.4 ng/ml and normal IGF-1 values matched for age and gender effectively exclude the diagnosis (Giustina et al, 2000). If either growth hormone and or IGF-1 are elevated, this should prompt referral to an endocrinologist for further evaluation.

The most specific diagnostic test is measurement of growth hormone levels in response to an oral glucose tolerance test. In normal subjects, growth hormone concentrations fall to 1 ng/ml or less within 2 hours post-ingestion of 75 g of glucose. In contrast patients with acromegaly fail to adequately suppress growth hormone post glucose-ingestion. The oral glucose tolerance test is also the gold standard for determining disease control after surgical treatment. The diagnostic cut off for growth hormone nadir post-oral glucose tolerance test depends on the assay used – this is much lower with the newer highly sensitive immunoradiometric or immunochemiluminescent assays (Melmed, 2006). Local policies should account for practice guidelines and the growth hormone assay used in the hospital laboratory. When a non-pituitary aetiology is suspected, serum growth hormone-releasing hormone should be measured

Serum IGF-1 concentration is the best single initial test. IGF-1 levels are elevated in virtually all patients with acromegaly and provide a good discriminator from normal individuals. Unlike growth hormone, IGF-1 does not exhibit diurnal variation, and IGF-1 concentrations reflect integrated growth hormone secretion during the preceding day or longer (Melmed, 2006). In normal subjects IGF-1 levels decline with age and differ between genders, thus age- and sex-adjusted normal ranges should be applied (Melmed, 2006). Renal dysfunction, malnutrition, uncontrolled diabetes mellitus, hypothyroidism and pregnancy affect IGF-1 levels and need to be accounted for to avoid diagnostic pitfalls (Melmed, 2006). The IGF-1 assays are not standardized and should not be used interchangeably. Despite these limitations, from a practical point of view, an elevated serum IGF-1 measurement is useful in the screening process, diagnosis and treatment monitoring of acromegaly.

Once the diagnosis of acromegaly has been biochemically established, the next step is magnetic resonance imaging of the pituitary gland (Reddy et al, 2010). Pituitary magnetic resonance imaging is the optimum imaging modality and can detect pituitary tumours as small as 2 mm, while providing details of the anterior and posterior pituitary lobes, allowing delineation the hypothalamus, the optic chiasm and the extent of local tumour invasion (*Figure 3*). Computed tomography can be used in cases for which magnetic resonance imaging is not amenable.

Acromegaly-associated comorbidities

The risk for development of acromegaly-associated comorbid conditions increases with the duration of clinical symptoms before diagnosis, the tumour size, the patient's age and the levels of growth hormone before and after treatment (Biermasz et al, 2005). The excess growth hormone or IGF-1 result in cardiac enlargement with left ventricular hypertrophy. With untreated prolonged disease cardiomyopathy and cardiac failure can develop. Other cardiovascular manifestations include hypertension, arrhythmias and increased prevalence of valvular disease, most commonly aortic regurgitation (30%) and mitral regurgitation (5%) (Biermasz et al, 2005).

Nasopharyngeal soft tissue swelling, macroglossia and pneumomegaly result in respiratory dysfunction. More than 50% of patients have obstructive sleep apnoea at diagnosis. Moreover the central effects of growth hormone itself on respiratory control may contribute to sleep apnoea (Rosenow et al, 1996).

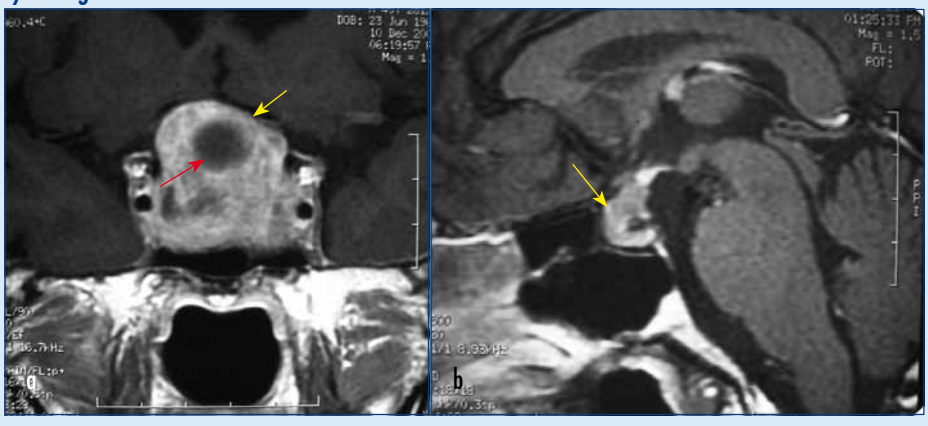
Enlargement of synovial and cartilage tissue results in early degenerative arthritis, affecting mainly the weight-bearing joints and spine, and kyphoscoliosis with associated functional disability (Lieberman et al, 1992; Biermasz et al, 2005). Carpal tunnel syndrome develops in 20–50% of patients as a result of soft tissue enlargement and median nerve oedema (Reddy et al, 2010).

Studies have reported increased risk of adenomatous colonic polyps in patients with acromegaly and higher risk of colonic neoplasia (Reddy et al, 2010). Prospective colonoscopy screening control studies indicate that the risk of colonic cancer in patients with acromegaly is twice that seen in the general population (Renehan and Shalet, 2002). The risk for other malignancies (lung, thyroid, breast) may also be increased (Reddy et al, 2010).

Disease monitoring

Serum growth hormone day curve, IGF-1 and growth hormone response to oral glucose tolerance test challenge are used for biochemical monitoring of the dis-

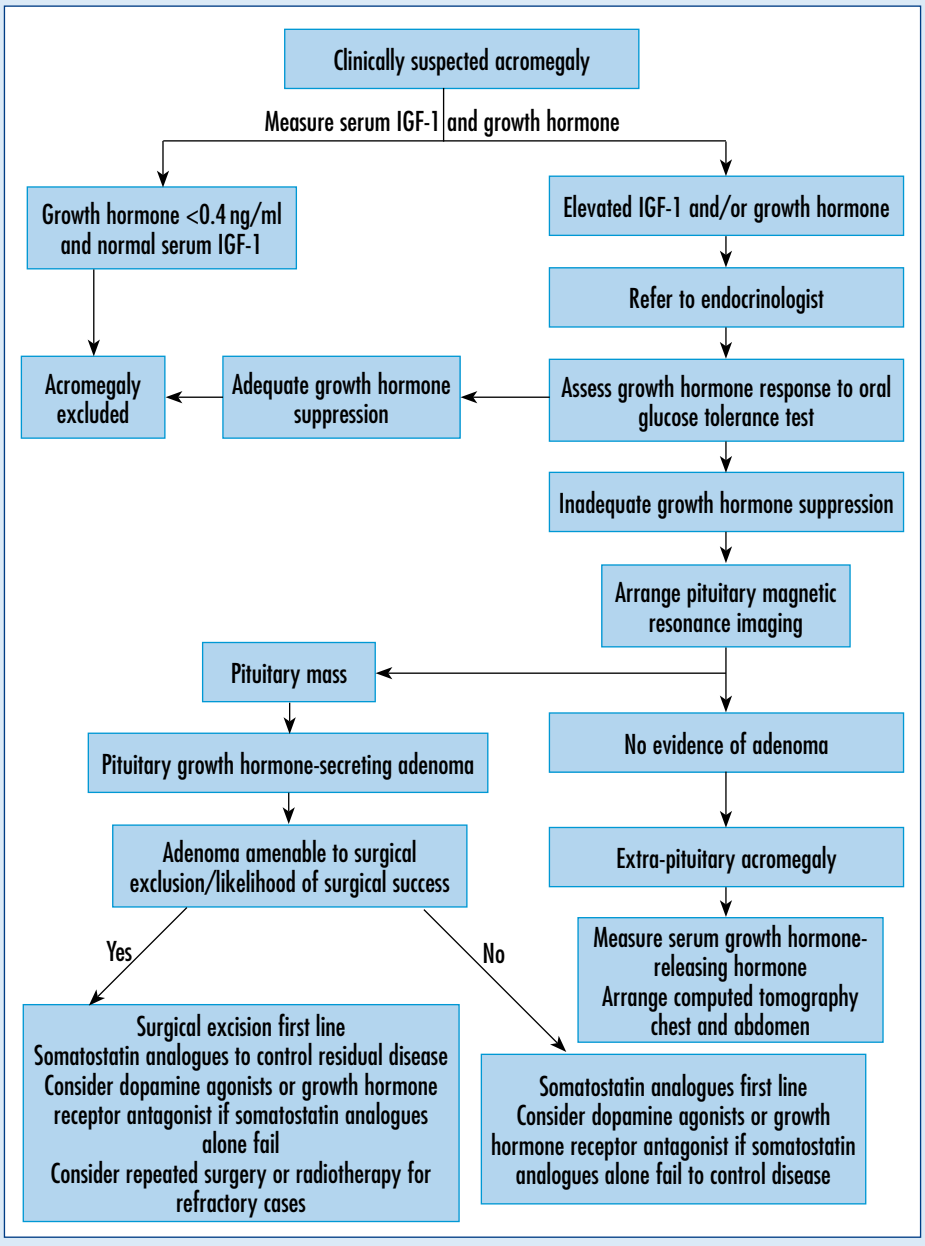
Figure 3. Pituitary magnetic resonance imaging post-gadolinium contrast (a) coronal and (b) sagittal T1-weighted views; large pituitary macroadenoma (yellow arrows) with suprasellar extension, optic chiasm compression and encroachment of the carotid arteries. The red arrow points at a central area of cystic degeneration.



ease. The frequency of these tests depends on whether the disease is in remission or remains active. Biochemical screening should be performed annually in patients with inactive disease. Fasting glucose, serum calcium and phosphate should be measured in all patients. The integrity of the other pituitary hormones needs to be assessed. Basal endocrine assessment includes 9 am cortisol, thyroxine, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone, testosterone and prolactin, while serum electrolytes with paired serum and urinary osmolality should be measured if diabetes insipidus is suspected. Dynamic tests to assess the pituitary–hypothalamic–end gland axis may be required. The decision to undertake pituitary gland re-imaging is guided by the biochemical assessment.

In all cases visual acuity and visual fields should be assessed at the initial consultation and fundoscopy performed to exclude papilloedema, optic atrophy or retinal venous engorgement. Patients with clinical symptoms and signs or with radiological evidence of optic chiasm compression require formal visual field perimetry or visual evoked responses.

Figure 4. Algorithm for investigating suspected acromegaly and treating confirmed acromegaly. IGF-1 = insulin-like growth factor 1.



Baseline echocardiography and colonoscopy should be arranged for all patients, with follow-up colonoscopies every 3–5 years. If there is clinical evidence of obstructive sleep apnoea polysomnography should be organized.

Prognosis

If untreated acromegaly reduces life expectancy by an average of 10 years (Rajasoorya et al, 1994). The overall mortality of untreated disease is double than normal and the most common causes of death are cardiovascular complications, respiratory disease and cancer (Giustina et al, 2000). The presence of complications, symptoms duration and old age increase mortality (Holdaway et al, 2004). Suppression of growth hormone with treatment has been shown to improve survival rates (Giustina et al, 2000). Therefore timely diagnosis and successful control of growth hormone hypersecretion with treatment are key to reduce mortality and improve disease prognosis.

Treatment of acromegaly

The treatment goal is amelioration of symptoms and normalization of the growth hormone or IGF-1 concentrations. *Figure 4* illustrates an algorithm for investigating suspected acromegaly and treating confirmed acromegaly.

Pituitary surgery

First-line treatment is hypophysectomy by an experienced pituitary neurosurgeon which results in growth hormone normalization in 70–90% of cases in patients with microadenomas (<1 cm in diameter) and in 45–50% in patients with macroadenoma (>1 cm in diameter) (Ahmed et al, 1999). Surgically-induced pituitary damage leads to transient or permanent hypopituitarism in up to 30% of patients (Colao et al, 2006).

Radiotherapy

Radiotherapy is generally used as adjuvant treatment when surgery has failed to cure the disease. External beam radiotherapy is administered over a period of several weeks (Jenkins et al, 2006). Several centres are using stereotactic radiotherapy which the gamma knife delivers radiation to the tumour target. Radiotherapy treatment slowly reduces IGF-1 levels and disease

control may take up to 15 years. Side effects include hypopituitarism, with 50% of patients developing deficiency in one or more pituitary hormones within 10 years of treatment local damage, and cerebrovascular disorders (Minniti et al, 2005).

Medical treatment

The pharmacological approach is used as second line to control residual disease following surgical excision of the adenoma and while waiting for radiotherapy to take effect. However, medical treatment can be given first line in cases of high surgical risk, or with adenomas not amenable to surgical excision.

More than 90% of growth hormone-secreting tumours exhibit wide expression of somatostatin receptors subtypes 2 and 5 (SST2 and SST5). Somatostatin receptor stimulation reduces growth hormone production. Octreotide and lanreotide are selective ligands for SST2 and SST5. Their depot formulations allow administration at 4–6-week intervals (given intramuscularly). Somatostatin analogues induce biochemical control and tumour shrinkage in 50–60% of cases (Murray and Melmed, 2008). Common side effects include gastrointestinal disturbances, gall bladder sludge formation or asymptomatic gallstones and blood glucose rise in some patients.

Dopamine agonists were the first medical treatment used for acromegaly before the development of somatostatin analogues. Despite the poor efficacy of the first dopamine agonists treatment with the newer dopamine agonist cabergoline appear to be more promising. Currently dopamine agonists are used mostly in combination with somatostatin analogues or alone when maximum dose of somatostatin analogues has failed to control the disease (Manjila et al, 2010).

Pegvisomant is a growth hormone receptor antagonist administered as a daily subcutaneous injection. Several studies have demonstrated pegvisomant to be the most effective medical therapy to date and have established its long-term efficacy in the treatment of acromegaly (Manjila et al, 2010). Pegvisomant cross-reacts with growth hormone assays and pituitary-derived growth hormone increases, hence growth hormone cannot be used to monitor patients treated with pegvisomant (Manjila et al, 2010). The major drawback of pegvisomant is the need for daily injections, as opposed to depot somatostatin analogues. Currently pegvisomant use is limited to cases resistant to somatostatin analogues, either as a sole agent or as an additive agent.

Conclusions

Acromegaly is a rare clinical condition, associated with significant morbidity and mortality. The disease is characterized by insidious onset, slow progression and usually presents with non-specific symptoms; thus, often being subject to considerable delay in diagnosis. Increased awareness of the condition by clinicians coupled with a low index of clinical suspicion is key to timely diagnosis and outcome optimization. BJHM

Conflict of interest: none.

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KEY POINTS

- Patients with acromegaly often present with non-specific symptoms, and a high index of clinical suspicion is required for timely diagnosis.
- In more than 99% of cases acromegaly is caused by a growth hormone-secreting pituitary adenoma.
- Initial screening should be performed by serum random growth hormone and insulin-like growth factor 1 measurement.
- Lack of suppression of growth hormone post-oral glucose tolerance test challenge confirms the diagnosis.
- Magnetic resonance imaging is the best imaging modality for pituitary tumour localization.
- Transsphenoidal hypophysectomy is the first line of treatment.