Acromegaly: an early diagnosis may improve outcomes

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Acromegaly often presents insidiously, remaining undiagnosed for many years. Earlier diagnosis and effective treatment are important to minimise disease-associated morbidity and mortality.

Key points

- **Acromegaly is commonly associated with a delayed diagnosis.**
- **Patients with acromegaly have significant disease-associated morbidity and mortality, particularly respiratory, cardiovascular, musculoskeletal and metabolic complications.**
- **Patients with acromegaly should be managed within a centre where there is a multidisciplinary team available.**
- **Good biochemical control and regular screening for complications are important long-term goals in the management of patients with acromegaly.**

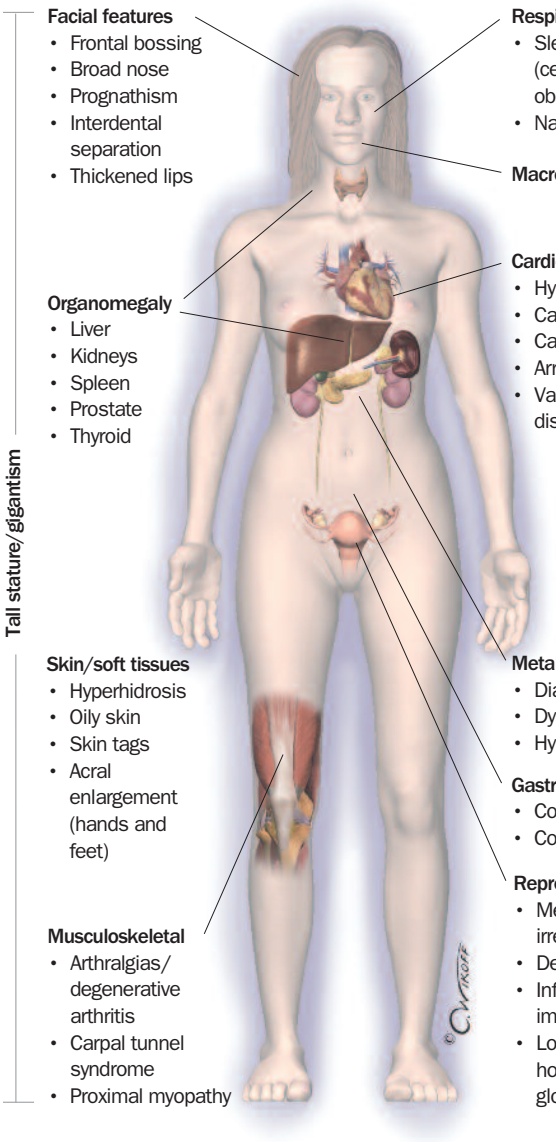

Figure 1. The clinical features of acromegaly.

What is acromegaly?

Acromegaly is a rare clinical condition caused by excess growth hormone (GH) secretion. Gigantism occurs where GH excess develops during childhood or adolescence before the fusion of the epiphyseal growth plates. Nearly all cases of acromegaly are caused by GH-secretory pituitary adenomas and 25% of these tumours co-secrete GH and prolactin.[1]

More than 75% of GH-secretory pituitary adenomas are macroadenomas at diagnosis.[1] Although the vast majority are benign and slow-growing, a significant proportion (45 to 55%) can become invasive.[2] Malignant adenomas, however, are extremely rare (less than 0.2% of pituitary tumours).[3] Younger patients tend to have larger, more aggressive tumours.[4]

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Figure 2. Historical pictures showing the progression of acromegaly in a man from 29 years of age to 42 years.

Although most cases (about 85%) of acromegaly are sporadic,[4] acromegaly may occur in association with a familial syndrome such as familial isolated pituitary adenoma, multiple endocrine neoplasia type 1, McCune-Albright syndrome or Carney syndrome.[1]

How common is it?

The annual incidence of acromegaly is estimated at approximately three to four cases per million persons per year, and the prevalence is 60 to 130 per million. However, acromegaly is largely clinically under-recognised.[4] The mean age at diagnosis is 40 to 45 years and it affects all races and both sexes.[4]

Why is it important?

Acromegaly is associated with significant morbidity, particularly respiratory, cardiovascular, metabolic and musculoskeletal complications of chronic GH excess. Acromegaly also confers an increased risk of premature mortality. Reported standardised mortality ratios range between 1.3 and 3.0,[5] with an average life expectancy 10 years below that of the general population.[4] Importantly, the risk of premature mortality is reduced if GH levels are maintained below 2.5 µg/L (7.5 mIU/L) and insulin-like growth factor-1 (IGF-1) levels are normalised,[6] highlighting the importance of early diagnosis and good disease control.

Pathogenesis and GH physiology

Pituitary adenomas arise from a series of genetic alterations that ultimately lead to cell transformation and the development of an adenoma. GH secretion by pituitary somatotrophs is stimulated by hypothalamic GH-releasing hormone (GHRH) and inhibited by somatostatin and negative feedback from IGF-1. GH stimulates the production of the peptide hormone IGF-1, which acts as a secondary messenger for GH. IGF-1 is produced in the liver and peripheral tissues, and is released into the circulation as well as having localised effects. IGF-1 is a principal regulator of cell proliferation and metabolism. The clinical manifestations of acromegaly occur due to both the actions of excess GH and IGF-1. For example, soft tissue overgrowth and enlargement of the hands and feet occur due to IGF-1 mediated stimulation of cell proliferation.[1]

When to suspect acromegaly?

Patients may present with features of acromegaly (see Figure 1) or symptoms due to tumour mass effects such as headache, visual field deficits, cranial nerve palsy and hypopituitarism. Due to the fact that the classic features of acromegaly develop very slowly over many years and the initial symptoms are often somewhat nonspecific, patients with acromegaly often go unrecognised for many years (Figure 2). In fact, it is common for the diagnosis to be made by a new doctor seeing the patient for the first time.

Patients with acromegaly may initially present with complaints such as headache, lethargy, arthralgias and increased sweating, which in isolation have a low probability of being due to GH excess but in the context of a constellation of other clinical features (Figure 1) may incur a greater suspicion of acromegaly. Changes in facial features are often most noticeable (e.g. frontal bossing, broad nose, thickened lips, prominent jaw) and old photos may be useful for comparison. Patients may have noticed a change in ring or shoe size rather than a change in the size of their hands or feet.

Certain conditions occur commonly as complications of acromegaly and if seen in combination with other symptoms and signs of acromegaly (Figure 1), then the IGF-1 level should be checked. In particular, these complications include hypertension (in 40% of cases), sleep apnoea (in 20 to 80% of cases), diabetes mellitus (in 19 to 56% of cases), and degenerative arthritis and carpal tunnel syndrome (in up to 50% of cases).

How is a diagnosis made?

An IGF-1 level should be the initial screening investigation in patients with symptoms and signs suggestive of acromegaly. A normal IGF-1 level (according to a sex- and age-matched reference range) effectively excludes acromegaly.[4] GH levels are highly variable due

to its pulsatile secretion, and food intake and exercise may influence levels. As such a random GH level is not recommended to screen for acromegaly.

Patients with an elevated IGF-1 level and features suggestive of acromegaly should be referred for an endocrinology review. The endocrinologist will usually proceed with a 75 g oral glucose tolerance test (OGTT). If GH does not suppress to below 0.33 µg/L (1 mIU/L) a diagnosis of acromegaly is confirmed.[4]

If an elevated IGF-1 level is found, a complete pituitary hormone profile (measurement of adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, free T4, free T3, luteinising hormone, follicle-stimulating hormone, oestradiol/testosterone, GH, IGF-1 and prolactin levels) should also be arranged. This will help in the assessment of hypopituitarism due to tumour mass effects and hyperprolactinaemia either due to prolactin co-secretion or stalk compression.

After a biochemical diagnosis has been made, an MRI scan of the pituitary (with gadolinium contrast) should be performed to determine the presence of a pituitary adenoma. MRI is also important to evaluate the tumour size, extent of invasion and relation to the optic apparatus and other adjacent structures. For those patients with a pituitary tumour close to the optic chiasm, a formal visual fields assessment should be performed by an ophthalmologist.

Management

The optimal approach to the management of acromegaly should occur in the context of a specialist pituitary multidisciplinary team. Ideally, the team should include clinicians from endocrinology, neurosurgery, radiation oncology, ophthalmology, radiology and anatomical pathology. The four key goals of treatment of patients with acromegaly are shown in the box on this page.

Surgical resection is recommended as primary therapy in most patients with acromegaly. In particular, primary surgical treatment is likely to be most appropriate for those patients with intrasellar microadenomas, noninvasive macroadenomas and tumours causing compressive symptoms. Medical management is traditionally used as second-line treatment or following surgery in patients with residual active disease. Radiotherapy is generally reserved as third-line therapy due to its lower efficacy rates and slow onset of effects. The 2010 Acromegaly Consensus Group revised guidelines for defining disease cure are shown in the box on this page.[7]

Goals of treatment in acromegaly

- Relief of symptoms and signs
- Tumour removal/relief of tumour mass effects, with preservation of normal pituitary function
- Prevention of disease-associated morbidity and premature mortality
- Normalisation of biochemical disease

Defining cure in patients with acromegaly[7]

- Insulin-like growth factor-1 level in the age-sex adjusted normal range
- Random growth hormone (GH) level <1.0 µg/L (3.0 mIU/L) or nadir GH <0.4 µg/L (1.2 mIU/L) on oral glucose tolerance test in postsurgical patients

Surgery: the first-line option

Patients with acromegaly should not be directly referred to a neurosurgeon because a thorough assessment by an endocrinologist is necessary before surgery is contemplated. Pituitary surgery should always be performed by a dedicated and experienced pituitary neurosurgeon as this has significant implications both in terms of surgical cure rates and risk of complications.[8] This can be ensured by first referring patients to an endocrinologist.

In most patients with acromegaly a transsphenoidal approach is used but rarely a transcranial approach may be required. More recently, some surgeons have adopted the use of transnasal endoscopic techniques. Cure rates for transsphenoidal surgery are negatively correlated with tumour size and invasiveness, with reported cure rates of 75 to 95% for intrasellar microadenomas, and 40 to 68% for noninvasive macroadenomas.[9] Recurrence rates have been reported at about 5.4% at 10 years.[10]

Surgical complications are reported in 2 to 15% of patients, most commonly cerebrospinal fluid rhinorrhoea and epistaxis. In addition, transient diabetes insipidus occurs in about 5% of patients.[11] Pituitary function improves in many patients following surgery; however, a proportion of patients develop postoperative hypopituitarism and rarely permanent diabetes insipidus.[12,13] Procedure-associated mortality has been reported in approximately 0.1 to 0.7% of cases; however, this risk appears to increase significantly in the elderly population and in particular those over the age of 80 years.[9,13,14] Postoperatively, patients should also have their pituitary function assessed and have an MRI to assess for residual disease.[15]

If surgery is not possible – what then?

If a patient's frailty and/or serious medical comorbidities confer excessive surgical risk, primary medical therapy is a good alternative to surgical intervention. When used as primary medical therapy, somatostatin analogues have been shown to induce biochemical remission in about 35 to 45% of affected patients based on IGF-1 criteria with significant reduction in tumour volume in about 40 to 75% of patients.[16-18] Additional benefits may include improvement in acromegaly-related conditions such as obstructive sleep apnoea.[15]

In cases in which tumour characteristics prevent complete resection, there is good evidence to support either use of primary medical therapy or primary surgical debulking later followed by medical therapy. Retrospective studies and more recently a prospective study have demonstrated better response rates to somatostatin

analogue therapy given after debulking than when given to the patient preoperatively.[16,19,20]

An alternative approach, for which there is growing support, is the use of medical therapy before surgery. Several small prospective trials have now demonstrated better surgical remission rates after pretreatment with somatostatin analogues.

What medical therapies are available?

Somatostatin analogues

Somatostatin is a hypothalamic peptide that inhibits secretion of GH. Somatostatin analogues are the most widely used form of medical therapy for patients with acromegaly. In Australia, octreotide LAR and lanreotide autogel are available and both appear to have similar efficacy in terms of achieving biochemical remission (about 60 to 70%) with average tumour size reduction of about 50 to 70%.[21,22]

The recommended starting dose of octreotide LAR is 20 mg administered as a deep intramuscular injection every four weeks. The endocrinologist may subsequently up- or down-titrate the dose within the range of 10 to 40 mg based on the patient's GH and IGF-1 levels. Lanreotide autogel is usually commenced at a dose of 60 mg administered as a deep subcutaneous injection every four weeks, with a dosing range of 60 to 120 mg.

Both injections can be quite painful for the patient. There can be practical difficulties with the reconstitution of octreotide LAR, which can cause the needle to block. Most patients have their somatostatin analogue injections given either by their GP or by hospital-based endocrine nurses, or via home-based injection programs.

Common side effects experienced with use of somatostatin analogues include cholelithiasis (in up to 20% of cases) and gastrointestinal upset. Use of somatostatin analogues also increase the risk of hyperglycaemia.[1,5]

Pasireotide (SOM230) is a novel multireceptor-targeted somatostatin analogue, but is currently not TGA approved. Early data suggest that this agent may offer additional efficacy over standard somatostatin analogue therapy.[23]

Cabergoline

Cabergoline monotherapy has inferior efficacy when compared with somatostatin analogues. Normalisation of IGF-1 levels has been reported in about 20 to 50% of patients. Patients with prolactin co-secretory tumours had a greater likelihood of response.[24] If biochemical control cannot be achieved on a somatostatin analogue alone addition of cabergoline can achieve normalisation of IGF-1 levels in about 50% of cases.[1] The recommended starting dose is 0.5 mg/week (orally), with subsequent up-titration to 1 to 4 mg per week, as tolerated. Nausea is the most commonly experienced side effect with cabergoline (in 30% of cases).

Pegvisomant

Pegvisomant is a GH-receptor antagonist that blocks the action of GH at the GH receptor. It appears to have similar efficacy to conventional somatostatin analogue therapy with regard to normalisation of the IGF-1 level (50 to 60%).[25,26] Addition of pegvisomant in patients with suboptimal control on somatostatin analogue monotherapy has been reported to achieve normalisation of IGF-1 levels in 95 to 100% of patients.[27,28] Unfortunately pegvisomant is not yet available in Australia (but can be shipped from overseas) and, although TGA approved, is not PBS funded (the cost of treatment is about $25,000 to $35,000 per annum) and as such is only used in very exceptional cases.

Radiotherapy

Concerns about the use of radiotherapy for acromegaly include:

- its slow onset of effects; it often takes years to achieve biochemical control
- hypopituitarism (over 50% of cases at 10 years)[1]
- damage to the optic apparatus and other surrounding structures
- secondary malignancy.

Evidence suggests that about 60% of patients achieve biochemical remission with use of radiotherapy after 10 years.[29] Compared with conventional external beam radiotherapy, stereotactic radiosurgery and gamma knife radiosurgery have similar efficacy, but with less exposure to surrounding tissues and reduced treatment times.[29]

Monitoring

Disease control

The 2010 Acromegaly Consensus Group guidelines recommend monitoring of patients with acromegaly every six to 12 months with MRI and bloods tests (GH and IGF-1 levels), even in well-controlled patients. In patients who have had good disease control for two to three years, the frequency of MRI may be reduced. OGTT is not helpful in monitoring therapeutic response while a patient is on somatostatin analogue therapy.[7] Patients with suboptimal disease control require more frequent endocrinologist input and review of management.[9]

Screening for complications

A complete anterior pituitary hormone profile should be checked regularly to screen for the development of hormone deficiencies that may require replacement, especially if the patient has had recent surgery or previous radiotherapy.

Metabolic complications (diabetes and dyslipidaemia) account for a significant proportion of patients with premature mortality. Sleep apnoea is also a common serious comorbidity due to a combination of obstruction from laryngeal soft tissue swelling and central sleep disturbance. Cardiovascular complications, in particular hypertension, are a predictor of premature mortality in patients with acromegaly.[30] Other cardiovascular complications include cardiac failure, arrhythmias and valvular heart disease.

Musculoskeletal complications are also frequently seen in patients with acromegaly and have a significant impact on quality

of life.[1] Surgical intervention may be required for patients with musculoskeletal complications (e.g. degenerative arthritis and carpal tunnel syndrome) and orthodontic or maxillofacial complications. It is suggested that such procedures ideally be performed after normalisation of GH and IGF-1 levels for at least six months.[31]

Colonic polyps commonly develop in people with acromegaly, postulated to be due to trophic effects of IGF-1 on the intestinal epithelium. There is about a twofold increased risk of colorectal cancer in affected patients. There are some data to suggest that acromegaly may also confer an increased risk of other malignancies, such as breast, lung and thyroid cancer.[32]

There are at present no comprehensive guidelines with regards to screening for complications in patients with acromegaly. However, some reasonable screening principles are outlined in the box on this page.[9,31]

Recommended approach to screening for complications of acromegaly[9,31]

Metabolic
- Hypertension: blood pressure should be regularly monitored, even in patients with well-controlled disease (suggested target of <130/80 mmHg)
- Dyslipidaemia: lipid studies (annually)
- Diabetes: fasting blood glucose level (annually)

Respiratory
- Sleep apnoea: sleep studies (polysomnography) at diagnosis then every five years in those with active disease, or as clinically indicated

Cardiovascular
- Echocardiography at diagnosis then every five to 10 years or as clinically indicated

Gastrointestinal
- Colonic polyps: at least one colonoscopy at baseline. Follow-up colonoscopies should be performed in patients with ongoing active disease. If a patient has had colonic polyps, he/she should subsequently be followed up according to the international guidelines for colon cancer
- Cholelithiasis (somatostatin analogues): abdominal ultrasound as clinically indicated

Musculoskeletal
- Carpal tunnel syndrome: regular monitoring for symptoms and signs of joint disease
- Degenerative arthropathy: regular monitoring for symptoms and signs of joint disease

Malignancy
- Screening according to general population guidelines
- Thyroid examination and thyroid function tests

Adapted from the 2009 Acromegaly Consensus Group guidelines[9] and the 2011 American Association of Clinical Endocrinologists guidelines.[31]

Useful web resources

- Australian Pituitary Foundation (www.pituitary.asn.au)
- Sydney Pituitary Collaborative Group (www.pituitaryresearch.com.au)

Fertility and pregnancy

Impaired fertility is relatively common in patients with acromegaly due to the effects of GH and IGF-1 excess on ovarian function, but also hypopituitarism and hyperprolactinaemia.[33]

During pregnancy, the normal pituitary increases in size by up to 45% due to oestrogen-mediated pituitary hyperplasia and oedema. Theoretically, GH-secreting tumours could increase in size during pregnancy, and predispose the patient to pituitary apoplexy due to increased pituitary vascularity.[33] Furthermore, there is some concern about using somatostatin analogues during pregnancy; however, small case series have not revealed any fetal concerns to date.[33]

It is therefore important that, before planning a pregnancy, a careful review is undertaken by an endocrinologist with regards to disease control and use of medications to minimise the risk to the woman and her child.

Role of the GP

GPs play an important role in the initial diagnosis as well as the long-term management of patients with acromegaly. Although medical and surgical management requires continued close involvement with an endocrinologist, screening and management of disease-associated complications is largely co-ordinated by GPs.

Conclusion

Acromegaly is a rare condition caused by GH excess and has significant associated morbidity and premature mortality. Diagnosis is frequently delayed owing to the fact that patients often initially present with insidious symptoms and signs. Good biochemical control is important to minimise the long-term sequelae of GH excess. Some useful web resources are shown in the box on this page.

Transsphenoidal surgery is the first-line treatment for most patients with acromegaly. Patients with refractory disease are usually treated with somatostatin analogues. In some cases, combination medical therapy or radiotherapy may be required. Regular screening for complications is an important element of the holistic management of patients with acromegaly and improved quality of life. **ET**

References

A list of references is available on request to the editorial office.

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