

# Acromegaly

## — treatment options and management

By **Anita Banerjee**, MBBS, MRCP, **Krishna Patel** MRPharmS and **Alison.M.Wren**, MBBS, MRCP

Acromegaly is usually treated by surgery to remove the pituitary adenoma, but adjunctive treatment with drugs and radiotherapy is also necessary. This article describes the treatment options and the importance of long-term monitoring



The hand of a patient with acromegaly (right) next to that of an adult male of average size

**A** cromegaly is an uncommon disorder that develops when the pituitary gland produces too much growth hormone (GH) during adulthood, usually as a result of a pituitary adenoma. It is characterised by a number of somatic, local and metabolic effects as described in the previous article (p273).

Management of acromegaly may include surgery, radiotherapy, and pharmacological therapy. Treatment is tailored to the individual and may differ depending on tumour size and response to therapy. First-line treatment has traditionally been transsphenoidal surgery (removal of the tumour through the sphenoid sinus) but primary pharmacological therapy with somatostatin analogues may be used in specific cases. This article describes the surgical, radiation and drug treatment options for the condition.

Acromegaly may remain undiagnosed for many years and therefore treatment may be delayed until years after onset of the disease. Studies show that patients with acromegaly who are untreated are more likely to suffer from hypertension, diabetes, stroke and myocardial infarction than the general pop-

ulation, and have a reduced life expectancy.<sup>1</sup> The management of a patient with acromegaly should be a multidisciplinary approach involving the endocrinologist, neurosurgeon, radiotherapist and neuroradiologist. The goals of the treatment are:

- To reduce GH production to normal levels
- To relieve the pressure that the pituitary tumour exerts on the surrounding areas which can cause headaches and disturbed vision
- To preserve normal anterior pituitary function
- To reverse or improve symptoms of acromegaly (eg, fatigue, hyperhidrosis)
- To reduce serum insulin-like growth factor -1 (IGF-1) concentration to within the reference range for the patient's age and gender
- To improve long-term survival

The treatment options available are often used in combination depending on the individual case. Treatment is monitored in terms of tumour size, biochemical control (serum GH and IGF-1 levels) and disease-related symptoms. Hypersecretion of GH is associated with a number of comorbidities including diabetes mellitus and hypertension, and patients should be monitored for evidence of these. These comorbidities should be treated with conventional drugs while the underlying cause is treated. The

drugs used to treat them may be reduced and stopped over time, if the GH excess is successfully treated. Panel 1, (p284) summarises the treatment options for the disease.

### — Pituitary surgery

Surgery is still considered the first-line treatment for acromegaly in most patients since it is usually caused by a benign, GH-secreting pituitary adenoma. The aim of surgery is to remove the pituitary tumour. The surgery is usually carried out by cleaving the mucosa off the nasal septum, providing access to the sphenoid sinus with subsequent removal of the sellar floor (where the pituitary gland sits). This is called the transsphenoidal approach and allows the surgeon to see the pituitary gland without having to perform a craniotomy. Transsphenoidal hypophysectomy has the dual advantage of improving symptoms caused by mass effects of the tumour such as headaches, visual field defects, and cranial nerve palsies as well as reducing or normalising GH and IGF-1 concentrations.

The success of the surgery depends on the ability and experience of the surgeon and on the size and extension of the mass. When a large number of individuals perform infrequent operations the outcome is usually poor. Outcome has been shown to improve when a single, dedicated pituitary surgeon is responsible for carrying out the procedure for all GH-secreting adenomas. One study

**Anita Banerjee** is specialist registrar, endocrinology and diabetes mellitus, **Krishna Patel** is lead pharmacist, medicine, and **Alison Wren** is consultant in endocrinology, all at Hammersmith Hospitals NHS Trust, London

found that when surgery was performed by a dedicated pituitary surgeon, the cure rate increased from 54 per cent to 86 per cent for microadenomas (tumours less than 10mm in diameter) and from 30 per cent to 52 per cent for macroadenomas (tumours over 10mm in diameter).<sup>2</sup> The biochemical criteria for cure were taken to be a basal GH of less than 5mU/L or nadir of less than 2mU/L in an oral glucose tolerance test (see p278) following pituitary surgery.

Small, non-invasive tumours carry a favourable surgical prognosis. Post surgery, it has been shown that the GH levels of 61 per cent of patients with microadenomas fell to below 5mU/L. In comparison, acceptable levels of GH were observed in less than 23 per cent of patients following removal of a pituitary macroadenoma.<sup>3</sup> In addition to pituitary tumour size, factors influencing post-surgical GH levels include the degree of extension of the tumour and the pre-operative serum GH levels.

Mortality from pituitary surgery is low (less than 1 per cent) in patients with adenomas. Mortality is associated with vascular complications, hypothalamic damage and meningitis. Complications of surgery include diabetes insipidus (which can occur in 5–15 per cent of cases but is usually transient) and cerebrospinal fluid rhinorrhoea. These problems are more common in

patients with macroadenomas. Deficiency of one or more pituitary hormone is also reported to occur post-operatively.<sup>4</sup> All patients undergoing transsphenoidal hypophysectomy should have an insulin tolerance test (unless contraindicated) six weeks after the operation to assess adrenocorticotrophin hormone and cortisol reserve. Contraindications to an insulin tolerance test include hypertension, ischaemic heart disease, history of epilepsy and cerebrovascular accident.

Incomplete tumour removal and thus continued tumour growth may be a problem with extended tumours and those which have invaded into the cavernous sinus. Tumour recurrence can also occur post-operatively. Periodic hormonal testing and repeat imaging studies are therefore important as part of follow up and long-term surveillance.

### — Pituitary radiotherapy

The radiotherapy treatment most frequently used in the treatment of acromegaly is an external beam, known as conventional fractionated irradiation. External beam radiotherapy is used both as a primary treatment and in combination with surgery or drug therapy. It is used for patients whose disease is not controlled by surgery or drugs

and sometimes as a primary treatment when surgery is refused or contraindicated. Treatment is tailored depending on patient characteristics, such as age and tumour size. Radiotherapy reduces serum GH levels and pituitary tumour size over many years after administration. Radiation treatment is given daily over four to six weeks and lowers serum GH by about 50 per cent over the first two years.<sup>5</sup> After 10 years serum GH levels are reduced to below 5mU/L in 80 per cent of patients.

Other approaches include heavy-particle (alpha particles or proton beams) radiation and stereotactic radiosurgery (eg, gamma-knife) using high dose, focused radiation. Pituitary implantation with radioactive 90-yttrium was formerly a treatment option for acromegaly, but has not been used for treatment in recent years.

The dose of radiation that can be delivered to the pituitary is limited by the presence of normal tissue within the treatment field. In particular, the dose delivered to the optic chiasm (where the optic nerves partially cross) must be low. In rare cases, radiotherapy may cause loss of vision, cranial nerve palsies and memory deficits. Stereotactic radiosurgery delivers a single, high dose of radiation to tumour cells while limiting the amount of radiation to the surrounding tissue, but requires specialist

equipment, and facilities for this type of radiosurgery are limited in the UK. There are studies that suggest biochemical remission is achieved earlier with focused radiotherapy than with conventional fractionated radiotherapy,<sup>6,7</sup> but no direct comparisons of different methods of pituitary radiation are available.

Since radiotherapy takes months or years to be effective, it is rarely used as primary treatment. Life-long surveillance is necessary for all individuals undergoing radiotherapy due to progressive loss of pituitary function. Patients treated with pituitary radiation usually develop deficiencies in one or more pituitary hormone.<sup>8</sup> It is estimated that after 10 years' follow-up more than 80 per cent of patients are deficient in two or more pituitary hormones. Gonadotrophin deficiency most commonly occurs first, followed by corticotrophin and then thyroid stimulating hormone deficiency. Once a patient has become deficient in one or more pituitary hormone, life-long hormone replacement treatment is necessary.

## — Pharmacological therapy

Pharmacological therapy has a role as both primary and adjuvant therapy in the treatment of acromegaly. It can be considered as primary therapy in patients who have an

unacceptable surgical risk, refuse surgery or who have adenomas that are inaccessible by surgery.

There are three classes of drugs available to treat acromegaly, which either inhibit GH secretion or inhibit its action. These are:

- Somatostatin analogues (eg, octreotide)
- Dopamine agonists (eg, cabergoline)
- Growth hormone receptor antagonist (pegvisomant)

## — Somatostatin analogues

Over the past 10 years, major progress has been made in the development of highly specific and selective pharmacological therapy for the management of patients with persistently active acromegaly: the somatostatin analogues.

Somatostatin is an inhibitory hormone released from the hypothalamus, which inhibits the release of GH. It also inhibits the release of thyroid stimulating hormone (TSH). Somatostatin analogues may decrease tumour size in approximately 30 per cent of patients.<sup>9</sup>

Somatostatin is also synthesised in the gastrointestinal tract and suppresses the release of various gastrointestinal hormones. The different actions of somatostatin are medi-

ated via specific membrane receptors. There are five somatostatin receptor subtype genes, SST1, SST2, SST3, SST4 and SST5. Several somatostatin agonists are known, each with different affinities for the respective somatostatin receptor subtypes.

**Octreotide** Octreotide was the first somatostatin analogue introduced for clinical use to treat GH excess. It has high affinity for SST2. The ability of octreotide to normalise serum IGF-1 is dependent on pre-octreotide serum GH levels and SST receptor expression by the pituitary tumour.

Octreotide is administered subcutaneously and initiates its effects within one hour. Its peak effect occurs within two to three hours after administration and lasts for five to eight hours. Therefore, as with all first generation somatostatin analogues, it must be administered three times a day. To overcome this problem, long-acting somatostatin analogues were developed, such as the long-acting release (LAR) form of octreotide. It is enclosed in microspheres of biodegradable polymer and administered by intramuscular injection every 28 days. The LAR preparation is well tolerated and effectively controls hormonal hypersecretion in most patients for 28–42 days. In some patients the dose administration interval may therefore be extended to six weeks rather than the

## Panel 1: A summary of the aims, advantages and disadvantages of different treatments for acromegaly

	Surgery	Radiotherapy	Dopamine agonists	Somatostatin analogues	Pegvisomant
<b>Treatment aims</b>	Complete resection Relief of mass effect Preservation of normal pituitary function	GH and IGF-1 normalisation Control of tumour growth	GH and IGF-1 normalisation Improve well-being	GH and IGF-1 normalisation Improvement in signs and symptoms Tumour size reduction	IGF-1 normalisation Control of symptoms
<b>Effectiveness determinants</b>	Surgical expertise Tumour size and extension Pre-surgery GH levels	Pre-surgery GH levels Tumour extension	GH/prolactin co-secreting tumours	Responders	Dose-response profile
<b>Advantages</b>	Potential cure in most patients Swift size reduction Debulking makes pharmacological therapy favourable	Non-invasive	No hypopituitarism Oral administration Rapid onset	No hypopituitarism Once monthly IM injection Tumour size reduction	Insulin sensitivity is improved in patients with glucose intolerance 90 per cent of patients have normal IGF-1
<b>Disadvantages</b>	Complete tumour removal may not be possible Hypopituitarism Adverse events as a result of major surgery	Delayed response Hypopituitarism Rare secondary tumours Rare visual defects	Low efficacy Side effects	Most patients do not achieve IGF-1 normalisation Injections Side effects	Daily subcutaneous injection Potential for tumour growth Rare elevation in liver function tests

monthly interval recommended by the manufacturer.<sup>10</sup>

Each patient's response to a short-acting formulation of somatostatin analogue should be assessed before a long-acting preparation is prescribed. If the serum GH level is less than 50 per cent of the baseline level after a single subcutaneous injection, then a long-acting formulation somatostatin analogue should be prescribed.

**Lanreotide** The second somatostatin analogue, lanreotide, is available as a long-acting (LA) formulation for intramuscular injections and an "Autogel" formulation for subcutaneous administration. Both preparations achieve similar disease control.<sup>11</sup> The LA formulation is administered every 10–14 days and the Autogel formulation is administered every 28 days. The administration interval may need to increase or decrease depending on the response.

### — Dopamine agonists

In healthy individuals dopamine stimulates GH release. However, in patients with acromegaly it inhibits GH secretion. About 30 per cent of all acromegaly cases consist of adenomas that secrete both GH and prolactin, and dopamine agonists typically achieve a favourable response in these type of

adenomas. Treatment with dopamine agonists should therefore be considered in acromegaly patients with hyperprolactinemia.

A number of dopamine agonists have been used as adjuvant therapy for patients with acromegaly — bromocriptine, cabergoline, pergolide, lisuride and quinagolide. Bromocriptine and cabergoline are the most widely used. However, dopamine agonists are not the drug therapy of choice in acromegaly since only a minority of patients treated with these drugs achieve normal circulating GH and IGF-1 levels.

**Bromocriptine** Bromocriptine has been used to treat acromegaly since the early 1970s and it was in 1974 that Chiodini and colleagues showed that administration of the dopamine agonist reduced GH levels in patients with the disease.<sup>12</sup> Bromocriptine is the only dopamine agonist licensed for use in acromegaly. It is licensed as adjunctive therapy to surgery and/or radiotherapy to reduce circulating GH levels in the management of patients with the disease. However, its effects on GH are modest, reducing plasma serum levels to below 10mU/L in less than 20 per cent of patients and normalising IGF-1 levels in less than 10 per cent of patients.<sup>13</sup> Bromocriptine also leads to tumour shrinkage in 20 per cent of patients.

Despite limited improvement in biochemical markers, most patients experience improvements such as decreased soft tissue swelling and reduced perspiration.

Bromocriptine is a short-acting agonist and is taken orally in divided doses, two to four times a day. Doses of up to 15–20mg per day must be administered in order to achieve effectiveness but side effects are more common with higher doses. Common side effects are nausea, vomiting and postural hypotension on initiation of treatment. Other side effects include dizziness, headache, nasal congestion, constipation, abdominal cramps and mood and psychological disturbances. These can be minimised by starting with a small dose (eg, 2.5mg) at night and increasing the dose every two to three days until the effective dose is achieved.

**Cabergoline** Cabergoline, a newer dopamine agonist, has been shown to be more effective than bromocriptine in addition to being better tolerated, although it is not licensed for the treatment of acromegaly. It is a longer acting dopamine agonist and is orally administered. The effect of long-term administration of cabergoline in 64 unselected patients with acromegaly has been evaluated.<sup>14</sup> A sub-group of 16

patients had GH/prolactin co-secreting adenomas. Treatment with cabergoline normalised plasma IGF-1 levels (to below 300µg/L) in approximately 40 per cent of patients. The weekly dose of cabergoline ranged from 1mg to 1.75mg and was well tolerated. A further increase in the dose was only effective in one patient with GH/prolactin co-secreting adenoma. Slight gastrointestinal discomfort and orthostatic hypotension in a few patients at the beginning of therapy was reported. However, higher doses of cabergoline may be required in clinical practice.

Studies of other dopamine agonists such as quinagolide, pergolide and lisuride in the treatment of patients with acromegaly are limited, and comparative data on different dopamine agonists with respect to acromegaly are scarce.

### GH receptor antagonist

**Pegvisomant** To date pegvisomant is the only available member of a new class of drugs specifically designed to block the receptor sites for GH, thereby blocking GH actions. Pegvisomant is a genetically modi-

fied analogue of human GH and is a highly selective, competitive growth hormone receptor antagonist. It is licensed for the treatment of acromegaly in patients with an inadequate response to surgery, radiation or treatment with somatostatin analogues.

GH is a large molecule which causes dimerisation of two receptors. GH receptor dimerisation is a prerequisite for activation of the post-receptor signalling cascade and generation of GH action. Pegvisomant binds to one GH receptor and prevents dimerisation, thus preventing GH from inducing IGF-1 synthesis in target organs. Unlike the

## Panel 2: Summary of pharmacological treatment of acromegaly

	Dose	Common side effects
<b>Dopamine agonists</b>		
Bromocriptine	Initially 1–1.25mg orally, at bedtime Increase gradually to 5mg every six hours	Nausea, vomiting, constipation, headache, drowsiness, nasal congestion, postural hypotension. With high doses; confusion, psychomotor excitation, hallucinations and rarely vasospasm of the fingers and toes, particularly in patients with Raynaud's disease
Cabergoline (unlicensed)	Weekly doses of 1–1.75mg orally have been used in studies	As above
<b>Somatostatin analogues</b>		
Octreotide	100–200µg three times a day by subcutaneous injection	Gastrointestinal disturbance including anorexia, nausea, vomiting, abdominal pain, abdominal bloating, flatulence, loose stools, diarrhoea and steatorrhoea, gallstone development, impaired post-prandial glucose tolerance, pain/irritation at injection site, and rarely hepatitis and transient alopecia
Octreotide long acting release (LAR)	A test dose of octreotide 50–100µg by subcutaneous injection is recommended if subcutaneous octreotide has not previously been given. Treatment with octreotide LAR may be started on the day after the last dose of subcutaneous octreotide. Treatment should be started with 20mg octreotide LAR intramuscularly at four-week intervals for three months. Subsequent dose adjustment should be based on GH and IGF-1 levels and clinical symptoms	As above
Lanreotide LA	Initially 30mg every 14 days by intramuscular injection. Interval decreased to 7–10 days according to response	As above
Lanreotide Autogel	Initially 60mg every 28 days by subcutaneous injection, adjusted according to response	
<b>Growth hormone antagonists</b>		
Pegvisomant	Initially 80mg daily by subcutaneous injection, then 10mg daily, increased in steps of 5mg daily according to response. Maximum dose 30mg daily	Nausea, vomiting, constipation, abdominal distension, dyspepsia, flatulence, diarrhoea, elevated liver enzymes, pain at injection site, headache, arthralgia, myalgia, peripheral swelling, sleep disorder, hypercholesterolemia, weight gain, hyperglycaemia, hunger

other types of pharmacological therapy for acromegaly, pegvisomant does not reduce GH levels but normalises IGF-I levels. Pegvisomant has a directly proportional dose-response profile since increasing amounts of the drug occupy a greater percentage of possible binding sites. Therefore, the dose can be tailored to individual patients based on serum IGF-1 response and clinical symptoms. It is administered by daily subcutaneous injection.

A 12-week, double-blind, placebo controlled study of 112 patients with acromegaly showed that pegvisomant therapy significantly decreased IGF-1 concentrations and improved the signs and symptoms of acromegaly.<sup>15</sup> Treatment with 10mg, 15mg and 20mg pegvisomant resulted in normalised IGF-1 concentrations in 54 per cent, 81 per cent and 90 per cent of patients, respectively. Pegvisomant was well tolerated and the incidence of side effects was similar in the placebo group and all three pegvisomant groups. The long-term effects of this agent on pituitary tumour growth are not known and tumour size must be monitored since continued growth may occur. Further evaluation of safety is also needed as elevation of liver enzymes have been reported in some patients while on pegvisomant.

A summary of the pharmacological therapies for acromegaly is shown in Panel 2 (p287).

## Long-term management

Whichever treatment is chosen initially, patients with acromegaly should be monitored long-term in the following areas:

### Clinical manifestations of acromegaly

Symptoms such as headache and soft-tissue enlargement of the face, hands and feet should improve with treatment. GH secreting adenomas present with headaches in 65 per cent of cases.<sup>16</sup> Hypophysectomy improves headaches in 49 per cent of patients but may exacerbate them in 15 per cent of cases.<sup>17</sup> Post-hypophysectomy headaches associated with GH secreting adenomas are common. The standard treatment of such headaches includes dopamine agonists and somatostatin analogues.<sup>18-21</sup>

### Serum concentration of GH and IGF-1

The serum concentration of GH either in response to ingestion of glucose solution (in the OGTT) or measured as a profile throughout the day (GH day curve) and/or the blood concentration of IGF-1 should be measured to determine whether the disease is controlled. These are the best objective tests to determine whether treatment has been successful.

**Hormone replacement therapy** The production of other hormones produced by the pituitary gland may decrease after surgery or radiotherapy. Life-long hormone

replacement therapy may be required to correct any deficiencies, which may include treatment with hydrocortisone, levothyroxine, antidiuretic hormone and sex hormones. Patient should be advised to carry a steroid card and to wear a medical alert bracelet if they are on cortisol replacement therapy, and should be reminded at intervals of the sick day rule (ie, increasing their steroid dose when they have a minor illness or are undergoing surgery).

## Conclusion

Acromegaly is a rare, chronic and debilitating disease which is associated with increased morbidity and mortality if left untreated. After diagnosis, the treatment is traditionally surgical resection of the responsible pituitary adenoma. An experienced pituitary surgeon should be selected for this operation. Complete resection is not always possible so adjunctive therapy with drugs and sometimes radiotherapy is necessary. The options for radiotherapy or primary drug therapy may be suitable for some patients in whom surgery is not expected to be curative, or who decline or are unfit for surgery. Improved disease awareness and targeted screening is required as timely diagnosis and appropriate treatment are crucial for reducing the debilitating symptoms of acromegaly. Long-term follow up of disease activity and comorbidities in diagnosed patients is important. A better understanding of acromegaly at the molecular level may provide novel approaches to therapy and possible cure of this disease in the future.

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## Correction

Krishna Patel was lead author, and not as listed.