Modern treatment of acromegaly

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Acromegaly is an endocrine disorder characterised by increased morbidity and mortality. It is usually caused by a growth hormone secreting pituitary adenoma and is manifested by a variety of clinical features. Surgery is usually the treatment of choice, however over the last few years, several new methods of treatment have been developed. A recent consensus on the targets for treatment has led to multiple studies being conducted to assess the efficacy of the currently available options. This review examines the evidence for and against these treatments.

Acromegaly is a clinical condition that results from chronic secretion of abnormally high amounts of growth hormone after fusion of the epiphyseal plates leading to an increased production of insulin-like growth factor-1 (IGF-1). It is usually caused by a growth hormone secreting anterior pituitary adenoma. Forty percent of patients carry a mutation in the α-subunit of the Gs protein coupled with the growth hormone-releasing hormone (GHRH) receptor (gsp+ve). It affects 40–60 people per million with an annual incidence of 3–4 per million. It is associated with increased morbidity and mortality with mortality being 2–3 times that of an age and sex matched normal population. This is due to an increased risk of cardiovascular, respiratory and gastrointestinal disease. Acromegaly is characterised by multiple signs and symptoms; common features include enlargement of bones and soft tissues, hyperhidrosis, lethargy, arthralgia, and headaches and in severe cases visual field defects. On average patients present around the age of 45 years with 75% of them having a macroadenoma at the time of diagnosis. Pierre Marie first defined it as a syndrome in 1885 and in 1909 Harvey Cushing performed his first operation for acromegaly. Since then several new methods of treatment have been developed but transsphenoidal surgery remains the primary treatment of choice. In the last few years a number of new medical treatments have been introduced with promising results such as long acting somatostatin analogues and growth hormone receptor antagonists.

Various targets for treatment have been used in the past but the current consensus is to aim for a nadir growth hormone level of less than 1 µg/l after an oral glucose tolerance test and a normal IGF-1 level for age and sex. There is also a general agreement that a basal growth hormone level below 2.5 µg/l is an acceptable target to consider the patient cured. This is mainly based on the results of several studies, which have shown that the mortality rate of patients with acromegaly is similar to that of the general population when growth hormone levels below this level are achieved. 

SURGICAL THERAPY

Surgery is the first line treatment for most patients with acromegaly. Transsphenoidal selective adenomectomy is the procedure of choice. On rare occasions craniofacial surgery may be needed when suprasellar extension prevents the transsphenoidal approach. The cure rate of surgery is about 80% for microadenomas and 40% for macroadenomas with a recurrence rate of about 5%–10%. Tumour size and preoperative growth hormone levels play an important part in determining the outcome of surgery. In a study by Kreutzer et al 37 acromegalic patients were analysed retrospectively using the new criteria for disease control. All patients included had transsphenoidal surgery as their primary treatment; the short term remission rate was 48.8% at six weeks increasing to 66.7% after 12 months or more (mean 37.7 months). Tumour size reduction was significantly greater in patients with persistent or resistant acromegaly. Patients with mixed growth hormone/prolactin cells and macroadenomas had the lowest remission rate. In another study 59 patients who had transsphenoidal surgery by one neurosurgeon were followed up for at least 10 years (10–22 years), using a random growth hormone level below 2.5 µg/l as a remission criterion; 61% achieved early postoperative remission. This was closely related to preoperative serum growth hormone levels. Forty percent of patients remained in remission after a mean of 16 years. Swearingen et al followed up 149 patients for a mean of 7.8 years after transsphenoidal surgery; the cure rate was 91% for microadenomas and 48% for macroadenomas. There was a 6% and 10% recurrence rate after 10 and 15 years respectively compared with 5.4% after a mean of 5.4 years in a different study involving 115 patients.

Kaltas et al found that tumour size, the degree of hypopituitarism, growth hormone and prolactin levels but not IGF-1 levels were useful factors in predicting the outcome of surgery. In addition, the mean growth hormone levels were more reliable indicators of surgical outcome and disease activity when compared with random growth hormone and/or IGF-1 levels.

The effect of preoperative octreotide has been assessed in a number of studies with variable results.
Somatostatin analogues

Growth hormone secretion from the pituitary gland is normally regulated by the stimulatory effect of GHRH and inhibitory effect of somatostatin, plus a feedback mechanism from IGF-1. Growth hormone secretion by tumour cells in acromegaly usually retains a high sensitivity to the inhibitory effect of somatostatin. Most tumours contain a large number of high affinity somatostatin receptors, which are diffusely distributed over the adenoma.52 Five subtypes of the human somatostatin receptor have been cloned. Subtype 2 is related to the antimitic effect of somatostatin in some cells, and the inhibition of cell proliferation is mediated by subtype 5.53 This forms the basis for using octreotide and lanreotide, which are long acting somatostatin analogues and bind with high affinity to these 2 subtypes of the receptor. Octreotide was the first medical treatment for acromegaly to be effective in a large proportion of patients. However because of the high doses needed and the fact that it is administered three times daily subcutaneously it is less convenient for the patients. It has now been replaced with sustained release forms of somatostatin analogues such as octreotide LAR and lanreotide SR. Lanreotide SR is usually given in a fixed dose of 30 mg intramuscularly every seven, 10, or 14 days while octreotide LAR is given intramuscularly every 28 days in a 10, 20, or 30 mg dose. Several studies have assessed the efficacy and tolerability of these two drugs, with success rates ranging from 45%–65%. The main adverse effects of somatostatin analogues are diarrhoea, nausea, abdominal pain, and pain at the injection site. Gallstones, usually asymptomatic and detected by ultrasonography, develop in 3%–12% of patients.24,25 This variability might be related to environmental, racial, and dietary factors. The development of gallstones is most likely due to the inhibition of both gall bladder emptying and cholecystokinin secretion.26 Tumour shrinkage occurs in 13%–36% of cases.

Starting with lanreotide SR, in a multicentre study involving 66 patients with active acromegaly all of whom apart from three had received at least one form of treatment in the past, 45% achieved a growth hormone level below 2.5 µg/l and 44% a normal IGF-1 level on lanreotide 30 mg intramuscularly. Tumour shrinkage of at least 25% was achieved in five out of 14 patients and symptoms improved by more than 50%.26 In a similar study involving 58 patients, most of whom had undergone pituitary surgery in the past, lanreotide PR was given for 12 months. At the end of one, six, and 12 months of treatment plasma growth hormone levels below 2.5 µg/l were achieved in 22%, 33%, and 41% respectively.27

In a two year follow up study by Balandelli et al, 118 patients were treated with lanreotide SR, 23 were de novo patients.27 The de novo patients showed a better response rate than the previously irradiated or operated on patients with fasting growth hormone levels below 7.5 µg/l and normal IGF-1 levels achieved in 78% and 70% of them respectively. This may simply be due to the de novo group containing patients with tumours more sensitive to lanreotide, or radiotherapy and surgery may result in changes rendering the tumour less responsive. On the other hand a follow up study of 31 patients treated with radiotherapy showed that patients on octreotide at the time of irradiation achieved normal levels of growth hormone and IGF-1 at a much longer interval than patients not on octreotide suggesting a radioprotective effect of somatostatin analogues.28

The effect of somatostatin analogues on the control of diabetes mellitus has been variable, ranging from improvement to worsening of control.16,29 Since they inhibit insulin secretion, deterioration in diabetes control might be expected, however its ability to delay the absorption of carbohydrates and inhibit the secretion of growth hormone and glucagon may prevent any significant effect on carbohydrate metabolism.30 There has been evidence that increasing the

MEDICAL THERAPY
Dopamine agonists

Dopamine agonists such as bromocriptine and cabergoline have been used with limited effect in the treatment of acromegaly. In one study three different dopamine agonists were assessed: quinagolide, cabergoline, and long acting depot bromocriptine. Thirty four patients were divided into three groups and followed up for 6–12 months. After six months only five out of 16 in the quinagolide group had a normal IGF-1 level and a growth hormone less than 2 µg/l in 67% of cases and include transient or permanent diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, haemorrhage, and cerebrospinal fluid leak. Surgical hypopituitarism is rare with microadenomas but affects 5%–10% of patients with macroadenomas.31,32

Box 1: Surgical therapy

- Treatment of choice for most patients.
- Cure rates about 80% and 40% for microadenoms and macroadenomas respectively.
- Transsphenoidal selective adenomectomy is the procedure of choice.
- Outcome is highly dependent on the skills and experience of the neurosurgeon.
- Safe with low morbidity and mortality.

...some suggesting a beneficial role while others showed no significant difference.12–14 In one study comparing 90 patients who had received preoperative octreotide to 50 who had not, no significant difference was detected and no transformation of a non-resectable adenoma to a transsphenoidally resectable adenoma was observed.15 The experience and skills of the neurosurgeon are especially important in determining the outcome of surgery.16,17 A study comparing the cure rates between surgery performed by one of eight different surgeons and that of a single dedicated surgeon, showed that the cure rate increased from 33% to 64%. The cure rate being 86% and 52% for microadenomas and macroadenomas respectively in case of the latter.18 Various results have been obtained from patients who have undergone a transsphenoidal operation for persistent or recurrent acromegaly after previous transsphenoidal surgery, with success being as low as 19% (three out of 16) in one study and as high as 73% (eight out of 11) in another.19,20 Transsphenoidal surgery for acromegaly is generally safe with low morbidity and very low mortality rate. Complications affect less than 3.5% of cases and include transient or permanent diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion, haemorrhage, and cerebrospinal fluid leak. Surgical hypopituitarism is rare with microadenomas but affects 5%–10% of patients with macroadenomas.31,32

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There has been evidence that combined treatment of cabergoline and lanreotide can be effective in selected cases resistant to somatostatin analogues alone.23 In addition, the oral route of dopamine agonist administration and its low cost are two main advantages when compared to somatostatin analogues.
dose of lanreotide SR to 60 mg from 30 mg results in a significant reduction in tumour size.\textsuperscript{9} Lanreotide SR has also been used in the treatment of a patient with a GHRH secreting carci-noid tumour with significant improvement in symptoms and growth hormone levels.\textsuperscript{33} A new long acting formulation of lanreotide (Lanreotide Autogel) has been assessed in the management of 107 patients with acromegaly previously responsive to lanreotide 30 mg intramuscularly. This new formulation is administered by a deep subcutaneous injection every 28 days. Thirty nine percent of patients on the subcutaneous formulation compared with 33% on the intramuscular formulation achieved growth hormone levels below 2.5 µg/l and normal IGF-1. The control of symptoms was comparable between the two treatments.\textsuperscript{32}

Octreotide LAR, the second main sustained release somatostatin analogue, was assessed in a European multicentre study which involved 151 patients who received 10, 20, or 30 mg intramuscularly at four week intervals and were followed up for 12 months. About 70% of patients achieved suppression of mean growth hormone levels below 2.5 µg/l. There was no increase in gallstone formation and it was very well tolerated with no adverse effect related withdrawals. There was a significant improvement in symptoms after the sixth injection.\textsuperscript{13} Similar results were achieved by a smaller study involving 14 patients followed up for 18 months.\textsuperscript{14} Kendall-Taylor \textit{et al} compared the effect of octreotide LAR with lanreotide SR on five patients.\textsuperscript{15} They were treated with each medication for six months with a wash out period in between. Four patients achieved growth hormone levels below 2.5 µg/l with each drug. Patients found octreotide LAR injections less painful and caused less diarrhoea. A growth hormone nadir of less than 1 µg/l in four patients was achieved only with octreotide LAR. Costwise the two drugs are comparable.

Some authors have suggested that somatostatin analogues may be used as a first line therapy. Newman \textit{et al} compared 26 de novo patients with 81 patients whom had undergone surgery and/or radiotherapy in the past.\textsuperscript{16} Both groups were started on octreotide and followed up for a mean of 24 months. There was no significant difference between the two groups with growth hormone levels falling at least 2 SD below the baseline in 70% and 61% of patients respectively. This is supported by the results of Baldelli \textit{et al} mentioned above.\textsuperscript{17} Bevan \textit{et al} have recently shown that somatostatin analogues can be effective as primary treatment in normalising growth hormone/IGF-1 and inducing tumour shrinkage especially in patients with a pre-treatment growth hormone level below 20 µg/l.\textsuperscript{18}

**Box 2: Medical therapy**

**Dopamine agonists**
- Mainly effective in tumours with positive growth hormone plus prolactin immunostaining.
- Oral route of administration and low cost.
- Less effective compared with other treatments.

**Somatostatin analogues**
- Success rate about 45%–65%.
- Can be effective as a first line therapy.
- Parenteral route of administration.
- Tumour shrinkage occurs in about 30% of cases.

**Growth hormone receptor antagonist**
- Genetically engineered analogue of human growth hormone molecule.
- 97% of patients achieve normal IGF-1 levels.
- Growth hormone levels remain high.
- Not yet available for commercial use.

**Radiation therapy**

Conventional radiotherapy has been used for many years in the treatment of acromegaly. With the introduction of pituitary microsurgery and new medical treatments, it is now mainly used as an adjuvant treatment and in patients unsuitable or refusing surgery. It is delivered in fractionated doses over five weeks with a total radiation dose of 4500–5000 cGy. Its main two disadvantages are the prolonged delay in achieving target growth hormone levels, sometimes up to 20 years, and the high incidence of hypopituitarism. However, further tumour growth is prevented in more than 99% of cases.\textsuperscript{46} In a study by Barrande \textit{et al}, 128 patients (104 had undergone transphenoidal surgery in the past) were followed up for a mean of 11.5 years after receiving conventional radiotherapy in a single centre.\textsuperscript{46} Basal growth hormone levels below 2.5 µg/l were achieved in 7% and 66% of patients after two and 15 years respectively. Pre-radiation growth hormone levels were
Box 3: Radiotherapy

Conventional radiotherapy
- Prolonged delay in achieving target growth hormone levels.
- High incidence of hypopituitarism.
- Tumour growth is prevented in more than 90% of cases.

Stereotactic radiosurgery
- Delivered in a single session.
- Especially useful for tumours invading the cavernous sinus.
- Contraindicated in suprasellar tumour extension.

Stereotactic radiosurgery is a modern form of radiotherapy that is delivered in a single session from a cobalt-60 source focused on the tumour. It is particularly useful for tumours invading the cavernous sinuses where the cranial nerves are much less susceptible to damage from radiation than the optic nerves. However, it is contraindicated in cases of suprasellar extension due to the risk of optic nerve or chiasm damage. In one study, 68 patients treated by GKS (most of whom as primary treatment), were followed up for 6–52 months. Normalisation of growth hormone was achieved in 40% of patients followed up for 12 months and 96% of patients followed up for more than 24 months. The tumour size shrank in 52% and 87% of cases respectively. In another study comparing GKS with conventional fractionated radiotherapy in patients who have had unsuccessful surgery in the past, the mean time for simultaneous normalisation of growth hormone (<5 μg/l) and IGF-1 was 1.4 years for the GKS group compared with 7.1 years for the fractionated radiotherapy group. Longer follow-up studies are needed to assess the long term efficacy and adverse effects of GKS.

Conclusion
Acromegaly is a serious disease characterised by increased morbidity and mortality. Several forms of treatment are available and with the introduction of new criteria for cure, multiple studies have been conducted to review the efficacy of these treatment modalities. Despite the development of new drugs in the last few years and the use of GKS, transsphenoidal surgery remains the primary treatment of choice for most patients. The importance of a dedicated and skilled neurosurgeon cannot be understated. However medical and radiotherapy still have an important role in the treatment of acromegaly especially in patients who are resistant to, refuse, or have recurrence after surgery. The main drawbacks of radiotherapy are the long interval between treatment and cure and the high incidence of hypopituitarism. New medical treatments have shown promising results with some success in predicting long acting somatostatin analogues as a first line option. Pegvisomant, which is not yet available for commercial use, has shown very good response rates. However because it blocks the actions of growth hormone rather than addresses the source of the problem, it is less favourable as a primary choice. There is also some concern about the possibility of tumour enlargement during long term therapy especially in patients who have not received radiotherapy in the past. Dopamine agonists, although less effective, are especially useful in patients with growth hormone/prolactin cosecreting adenomas, knowing that these patients have low response rates to surgery. Tumour size and growth hormone levels are important factors in predicting the outcome of treatment. As patients usually present with a macroadenoma at the time of diagnosis, most will need more than one form of treatment to achieve safe levels of growth hormone and symptom control.

SELF ASSESSMENT QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES)

Q1. Acromegaly:
(A) Results from abnormally high serum levels of growth hormone before fusion of the epiphyseal plates.
(B) 90% of patients carry the (gsp +ve) mutation.
(C) Hyperhidrosis and arthralgia are common features.
(D) Patients usually present in the fifth decade of life.
(E) 75% of patients present with a microadenoma.

Q2. Surgical therapy for acromegaly:
(A) Transsphenoidal selective adenomectomy is the procedure of choice.
(B) The cure rate is around 80% for macroadenomas.
(C) Preoperative growth hormone level is an important indicator of the outcome of surgery.
(D) Hypopituitarism is common after surgery.
(E) Complications include diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion.

Q3. Medical therapy for acromegaly:
(A) Dopamine agonists are effective in growth hormone/prolactin cosecreting adenomas.
(B) Dopamine agonists are administered subcutaneously.
(C) Somatostatin analogues are the drugs of choice for most patients.

Box 4: Key references

Pegvisomant normalises growth hormone levels in the majority of patients.

Vasoconstrictor is a growth hormone receptor agonist.

Somatostatin analogues:
(A) Are successful in 45–65% of patients.
(B) Asymptomatic gallstones develop in 30% of patients.
(C) Octreotide LAR is administered intramuscularly every 28 days.

Can be successful as a first line therapy.

Available in intramuscular and subcutaneous formulas.

Radiotherapy:
(A) Conventional radiotherapy is applied over several weeks.
(B) Normal growth hormone levels are usually achieved within six months of conventional radiotherapy.

Acromegaly is an uncommon complication.

GKS has shown promising results.

EKBs is especially useful for tumors invading the optic chiasm.

REFERENCES

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