Diagnosis and Management of Acromegaly in 2012

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Abstract

Acromegaly is an insidious disease that, in most cases, is a result of a pituitary adenoma that hypersecretes growth hormone (GH). The goals of therapy are to control excess GH secretion and tumour growth, and to limit, if not reverse, the long-term medical consequences and risk of premature mortality associated with acromegaly. Surgery is the preferred primary therapeutic option because it can lead to rapid reductions in GH levels and prevent mass effects from local tumor growth. Medical therapy, including somatostatin analogues, dopamine agonists, and the GH receptor antagonist pegvisomant, is used most often in an adjuvant, secondary role for patients in whom surgery has been unsuccessful. Radiation therapy is most commonly recommended in the setting of failed surgery and lack of adequate control with medical therapy. A role of primary medical therapy for *de novo* patients has been proposed, particularly with somatostatin analogues. Using a multimodality approach, successful management of the disease and associated consequences should be achieved in the majority of subjects.

Keywords

Acromegaly, somatostatin, pegvisomant, pituitary adenoma, cabergoline

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Acromegaly is an uncommon disorder that, in the vast majority of cases, is the result of a growth hormone (GH)-secreting pituitary adenoma. There is an estimated prevalence of 40–125 per million and an incidence of three to four new cases per million, although a more recent study in Belgium suggested a higher incidence of approximately 13 cases per 100,000.[1,2] Acromegaly is often diagnosed in patients in their early to mid-40s and has equal gender distribution.[3–5] Because the features of acromegaly progress in an insidious fashion, there is often a delay in diagnosis of approximately seven to 10 years after the estimated onset of symptoms.[6] Therefore, a pituitary macroadenoma (greater than 1 cm) is present in the majority of subjects.[7] Because tumours are often macroadenomas at the time of diagnosis, there may be a number of signs and symptoms related to local mass effects, including headache, visual field loss, ophthalmoplegia and hypopituitarism. Chronic GH and insulin-like growth factor 1 (IGF-1) hypersecretion can lead to soft tissue and bone overgrowth manifestations, medical co-morbidities and accompanying clinical features. Medical co-morbidites include arthropathy, cardiomegaly, sleep apnoea syndrome, type 2 diabetes, hypertension and colon polyps. In addition, acromegaly is associated with premature mortality, primarily owing to cardiovascular disease. Appropriate therapy of acromegaly can lead to improvement in these co-morbidities and reversal of the premature mortality risk.

Diagnosis of Acromegaly

The diagnosis of acromegaly begins with a clinical suspicion by the physician that the patient has this disease. Typical physical examination findings include hand and foot enlargement or facial bone enlargement and acral/soft tissue changes. Of note, subjects usually do not present with a chief complaint related to acral growth. In women, the most common presenting complaint is amenorrhoea.[4]

Biochemical testing involves measurement of GH and IGF-1. GH, produced by the somatotroph cells of the pituitary gland in a pulsatile fashion, circulates and stimulates hepatic secretion of IGF-1. In general, IGF-1 levels correlate with GH concentrations, especially with serum GH levels less than 20 ng/ml.[8] Because IGF-1 is an integrated measure of GH secretion and is subject to less serum variation than GH, a random IGF-1 measurement is highly useful for assessment of GH hypersecretion (see *Table 1*). Owing to the lack of agreement between assays and the lack of validated normal ranges for IGF-1,[9,10] the same assay should be used in the same patient for serial measurement.[11] A random GH measurement is not generally considered useful in diagnosis because of the lack of a well-defined normal or safe range, although a markedly elevated random GH level is certainly consistent with the disease. In one consensus statement, the presence of a random GH less than 0.4 ng/ml and normal IGF-1 was considered sufficient to consider the diagnosis highly unlikely.[12]

An oral glucose tolerance test (OGTT) is considered the gold standard test for acromegaly, and the inability to suppress serum GH to less than 1 ng/ml after glucose administration (75 g is recommended) is consistent with the diagnosis.[13–16] It is important to note that this cut-off nadir GH value is controversial, particularly given the development of more sensitive GH assays that lead to lower serum GH levels.[17] In a patient with signs and symptoms of acromegaly and an elevated IGF-1 value, an OGTT may not be necessary for diagnosis. In the setting of a clinical suspicion but discordant values, such as an

elevated IGF-1 and normal GH value (i.e., suppressible with OGTT), the subject likely has early stage acromegaly.[18]

After diagnosis of acromegaly, a magnetic resonance imaging (MRI) scan of the sella should be obtained to determine tumour size, location and invasiveness.[19] Visual field testing is performed if the tumour is touching or compressing the optic chiasm. A thorough ophthalmological examination should be performed if the patient describes diplopia and the tumour is invading the cavernous sinus.

Treatment

The goals of therapy for acromegaly are to control GH and IGF-1 activity, reduce tumour size and prevent local mass effects, reduce signs and symptoms of disease, prevent or improve medical co-morbidities, and prevent premature mortality. The primary mode of therapy is surgery. Medical therapy is mostly used in the adjuvant setting following surgery, although a role for primary medical therapy in selected patients with macroadenomas may be considered. Radiation therapy is largely relegated to an adjuvant role.

Surgery

Surgery is highly useful to debulk or resect the somatotroph adenoma, decompress local mass effects, rapidly lower or normalise GH and IGF-1 values, and obtain pathological tissue for further anlaysis. Surgery is recommended for all subjects with microadenomas because approximately 80 % or more of microadenomas are curable.[5] With an experienced surgeon, surgical cure rates for macroadenomas are approximately 40–50 %, likely reflecting the high prevalence of extrasellar extension and parasellar invasion of the cavernous sinus.[20–25] Surgery is recommended for all patients who have macroadenomas with associated mass effects. In patients who have macroadenomas without mass effects and with low likelihood of surgical cure, a role for surgical debulking of macroadenomas to improve response to subsequent medical therapy has been advocated, as has the use of primary medical therapy alone.[23] The transsphenoidal approach is the most common procedure, with craniotomy reserved for select cases involving large, extrasellar lesions. Transnasal endoscopic procedures offer improved visibility and are rapidly replacing microscopic techniques.[21]

Surgical efficacy can be assessed as early as post-operative day one, as demonstrated by Krieger et al.[26] where a fasting serum GH less than 2 ng/ml was associated with both a normal IGF-1 value and clinical evidence of disease remission at five years. Because the stress of surgery may stimulate the remaining normal gland to elevate GH levels, there is concern that a post-operative serum GH may have more limited prognostic value. The biochemical evaluation at 12 weeks post-operatively, including an IGF-1 level and an OGTT, is considered more valid in assessing surgical result.[27,28] In the post-operative setting, a lower nadir GH of less than 0.4 ng/ml has been suggested as a cut-off, although a 1.0 ng/ml value is generally used.[14,29] If there are discordant results, such as an elevated IGF-1 value but normal GH level, repeat testing may be warranted, particularly if there is a high clinical suspicion of persistent disease. Repeat imaging with an MRI scan is usually performed at least 12 weeks following surgery to allow for resolution of oedema and involution of Gelfoam® and fat packing.[30] Repeat pituitary hormone studies are performed at this time as well to assess for residual function.

Table 1: Diagnostic Tests in Acromegaly

Elevated serum IGF-1 (age- and gender-normalised)
GH nadir >1.0 ng/ml after oral glucose
Random GH <0.4 ng/ml and normal IGF-1 makes the diagnosis highly unlikely
Dedicated 'pituitary' MRI once there is biochemical confirmation

GH = growth hormone; IGF-1 = insulin-line growth factor 1; MRI = magnetic resonance imaging.

Is There a Role for Pre-operative Medical Therapy?

A role for medical therapy, particulary with somatostatin analogues, to improve surgical remission has been conjectured. In a multicentre study, six-month pre-treatment with octreotide long-acting release (LAR) (20 mg/month) resulted in surgical remission in 50 % of subjects with macroadenomas, compared with 16 % of those who underwent surgery without pre-treatment (p=0.02).[31] In a single-centre study, 98 subjects with macroadenomas were randomised to receive lanreotide for four months prior to surgery or to undergo surgery directly, and surgical remission was achieved in 49 % and 18 %, respectively (p=0.001).[32] These randomised studies suggest that pre-operative medical therapy may improve surgical remission rates. However, a limitation of both studies is the relatively low remission rates in the groups randomised to surgery alone. Further study is needed to determine whether medical therapy should be used routinely in the pre-operative setting.

Another consideration is the use of medical therapy pre-operatively to improve anaesthetic risk in the peri- and post-operative settings. Because intubation may be difficult and traumatic in up to 30 % of acromegagly patients, a role for medical therapy to reduce soft tissue swelling and reduce this risk has been considered.[33] In addition, subjects with acromegaly are at risk of cardiovascular disease, including hypertension and hypertrophic cardiomyopathy, with associated reduced ejection fraction.[34] Medical therapy may improve cardiovascular morbidities and surgical outcomes.[35,36] Use of medical therapy to reduce surgical risk is an important topic that deserves further research.

Medical Therapy

Medical therapy is largely used in an adjuvant role for patients with residual disease following surgery. However, primary medical therapy may be considered in subjects with macroadenomas and extrasellar involvement (especially involving the cavernous sinus) but no evidence of local mass effects such as chiasmal compression. In this situation, surgery will unlikely be curative and primary medical therapy *in lieu* of surgery may be considered.[37] In a recent study, three-quarters of patients had at least 25 % tumour shrinkage following 12 months of somatostatin analogue administration.[38] Primary medical therapy may also be considered in patients who are at high risk from surgery and according to patient preferences. In a subject who is undergoing primary medical therapy, surgery can always be reconsidered for tumour debulking to improve the response to medical therapy.[23]

For somatostatin analogue and dopamine agonist administration, serum GH and IGF-1 are the appropriate biochemical markers for following activity. Repeat testing is performed following dose changes at eight- to 12-week intervals.[27] GH suppression following glucose administration may be useful for monitoring the efficacy of medical therapy,[39–41] although a recent study questioned the use of this test in

this setting.[27] With administration of pegvisomant, serum IGF-1 only should be measured to monitor dose efficacy and GH levels should not be assessed. GH levels rise with pegvisomant administration and these GH levels have no impact on pegvisomant dosing.[42,43]

Dopamine Agonists

Bromocriptine and cabergoline are dopamine agonists that have been shown to be efficacious in the management of acromegaly. Both are orally administered and are less expensive than the other options, and therefore are often used as medical therapy. However, bromocriptine normalises IGF-1 levels in approximately 8 % of patients and high doses are often required.[44] Cabergoline, a more selective dopamine-2 receptor agonist, may be effective in up to 40 % of subjects with doses of 1.0–1.75 mg/week, although doses of up to 7 mg weekly may be necessary.[45,46] Subjects with modest elevation of their serum IGF-1 level may be the most responsive to dopamine agonist therapy. Some studies have suggested that co-secretion of prolactin may predict response, but this has not been supported by other studies.[47,48] Adverse effects of both bromocriptine and cabergoline include gastrointestinal upset, nasal congestion, fatigue, orthostasis and headache, but cabergoline may be better tolerated than bromocriptine. When used in higher doses (e.g., greater than 3 mg daily) in patients with Parkinson's disease, cabergoline has been associated with an increased risk of echocardiographic valvular abnormalities.[49] There are no definitive data that clearly link the use of cabergoline with cardiac valve disease in acromegaly, and the implication of this finding for patients with acromegaly remains unclear.

Somatostatin Analogues

Somatostatin analogues are the mainstay of medical therapy for acromegaly and are highly effective at improving both biochemical parameters and medical co-morbidities. There are two available somatostatin analogue formulations: octreotide and lanreotide.

Short-acting octreotide is administered at 0.05–0.3 mg subcutaneously up to three to four times a day. The advantages of short-acting octreotide include rapid action and a considerably smaller cost than the depot formulations. It is recommended that short-acting octreotide be administered for two weeks at a dosage of 0.1 mg three times daily prior to initiation of the octreotide LAR depot, to assess the response and tolerability of octreotide. However, this practice is not generally followed and, instead, one or two doses of short-acting subcutaneous octreotide may be administered to assess for significant toxicity.[50] Longer-acting depot preparations, including octreotide LAR (intramuscular) and lanreotide autogel (deep subcutaneous), are administered as monthly injections.

In a meta-analysis, depot formulations resulted in approximately 55 % normalisation of GH and 67 % normalisation of IGF-I levels.[51] Octreotide LAR and lanreotide autogel have similar pharmacological and efficacy profiles.[52] In cases where IGF-1 levels fall excessively, somatostatin analogues may be administered at six-week intervals or longer. Somatostatin analogue administration may result in tumour shrinkage. In one review of 14 studies using primary somatostatin analogue therapy, 36.6 % of patients had a significant (10 % to greater than 45 %) reduction in tumour size.[53] The efficacy of somatostatin analogues is a function of the somatostatin receptor subtype 2 density, although the presence of receptor subtypes is not routinely assessed.[54] Response to somatastatin analogues is inversely correlated with tumour size and degree of GH hypersecretion. The acute GH reduction following a single subcutaneous dose of octreotide and the degree of radiolabelled octreotide uptake have not been shown to be accurate in predicting biochemical remission.[55]

The most common adverse effects are abdominal cramping and diarrhoea, which are usually noted within the first 72 hours after each depot injection. Chronic somatostatin analogue use is also associated with an increased incidence of gallbladder sludge and gallstone formation, but these effects are not clinically significant in most patients.[51] Less frequently, hair loss, bradycardia, constipation, glucose intolerance and diabetes are described.

Pegvisomant

Pegvisomant is a recombinantly derived analogue of human GH that acts as a highly selective GH receptor antagonist.[42,43] Administration of pegvisomant leads to a reduction in IGF-1 levels, with a rise in circulating GH levels. Therefore, serum IGF-I, and not GH, is used to monitor the biochemical response to therapy. In a pivotal study involving a double-blind, placebo-controlled 12-week trial, daily subcutaneous administration of pegvisomant normalised IGF-1 in 89 % of cases.[42] In the follow-up extension study involving 152 patients treated for up to 18 months, IGF-I normalised in 97 % of patients.[43] Therefore, pegvisomant is highly effacious, and it may be particularly useful in improving glucose homeostasis in patients with glucose intolerance or overt type 2 diabetes.[56] More recently, there has been an increase in the use of weekly or twice-weekly formulations of pegvisomant, as less frequent administration may prove easier for patient use.[57]

Pegvisomant does not target the tumour, nor does it have tumour antiproliferative effects, giving rise to concern that its use may therefore lead to tumour growth. However, observational studies have shown tumour growth to be uncommon and, when present, it may reflect the presence of more aggressive tumours or rebound growth following recent discontinuation of a somatostatin analogue.[58] It is recommended that patients undergo monitoring with serial MRI scans; for example, at six-month intervals during the first year and then annually. Pegvisomant therapy is associated with abnormalities in liver function tests; in the German Pegvisomant Observational Study, transaminase levels greater than three times normal were noted in 5.2 % of subjects.[59] These transaminase elevations are usually asymptomatic and often transient and self-limiting, despite continued administration of pegvisomant.[59] Regular monitoring of liver function tests is recommended with discontinuation of the drug if these abnormalities are significantly elevated. Additional and uncommon adverse effects include an influenza-like illness, local allergic reactions and local lipohypertrophy.[60]

How to Manage the Patient with Somatostatin Analogue Resistance?

There are several management options for patients who are resistant to somatostatin analogues. One option is to increase the somatostatin analogue to a high-dose formulation (e.g., octreotide LAR 60 mg monthly), as this regimen may improve biochemical remission rates in an additional one-third of subjects.[61] In a patient with partial somatostatin analogue resistance, either pegvisomant or cabergoline could be added to the somatostatin analogue for additive effect. For example, the addition of pegvisomant to a

somatostatin analogue may result in biochemical control in up to 58 % of subjects and, through dose reduction of both the pegvisomant and somatostatin analogue, this regimen may have a cost benefit.[62] Addition of cabergoline to patients with partial response to a somatostatin analogue may lead to IGF-1 normalisation in about half of subjects,[63] although this benefit is generally noted in subjects with modest IGF-1 elevations. Another option involves surgical debulking of macroadenomas to improve the subsequent response to somatostatin analogues.[23] In a patient with full resistance to a somatostatin analogue, substitution of pegvisomant for the somatostatin analogue may be considered.[64] Finally, in a patient with somatostatin analogue resistance, consideration of radiation therapy may be warranted.[65]

Radiation Therapy

Radiation therapy is usually considered as an adjunctive therapy in subjects with active disease despite surgery and/or medical therapy, or to limit the need for lifelong medical therapy.[28,65,66] There are two main types of radiotherapy for patients with acromegaly: conventional fractionated radiotherapy and stereotactic radiosurgery.

Fractionated radiotherapy is typically administered in daily doses of 160–180 cGray (cGy) over a five- to six-week period up to a total dose of 4,500–5,000 cGy. Using strict remission criteria, such as a glucose-suppressed GH value of less than 1 ng/ml and a normal IGF-1 value, conventional fractionated radiation therapy results in biochemical cure in 10–60 % of subjects.[67–70]

Stereotactic radiosurgery includes a number of modalities, such as Gamma Knife® (Elekta AB, Stockholm, Sweden), CyberKnife® (Accuray Incorporated, Sunnyvale, CA, US) and a linear accelerator that delivers high-energy photons. Another option is use of proton particles.[71] In acromegaly, most experience with stereotactic radiosurgery involves Gamma Knife radiosurgery, which is usually delivered by a cobalt-60 gamma radiation source as a single treatment. With Gamma Knife radiosurgery, biochemical remission rates (without the need for medical therapy) are reported to be 17–50 % over a five-year follow-up period.[72–74] It has been suggested that time to remission is shorter with Gamma Knife radiosurgery than with conventional radiotherapy, although this is not entirely clear.[72,74–76]

Radiosurgery is generally considered if the tumour is a minimal distance from the optic chiasm, such as 5 mm, owing to concern about optic nerve injury.[77] Periodic withdrawal of medical therapy following radiotherapy should be performed for biochemical assessment. Somastatin analogues are often withheld at the time of radiation therapy because of concern that they may be radioprotective, although this finding is controversial, as it is not supported in all studies.[72,74,75,78]

The main limitation for radiotherapy is the development of hypopituitarism, which may occur in up to 50 % of patients after five to 10 years.[67,79] Radiation-induced secondary tumours and radionecrosis have been reported in fewer than 2 % of patients undergoing conventional radiotherapy.[80,81]

Managing Associated Medical Co-morbidities

The long-term management of acromegaly should also include screening and intervention for the associated co-morbidities. For example, cardiovascular co-morbidities, including hyperlipidaemia, diabetes and hypertension, should be monitored and treated accordingly. Serial colonoscopy should be performed in patients with polyps found at the baseline colonoscopy and those with persistent acromegaly.[82,83] In a subject with sleep apnoea syndrome, biochemical control may lead to improvement in the sleep disorder, although sleep apnoea may persist. Therefore, repeat sleep apnoea assessments should be performed and appropriate treatment offered.[84,85] Such monitoring should be performed in parallel with the acromegaly management.

Conclusion

Acromegaly is a multisystem disease that often requires multimodality therapy for control of the tumour, the GH hypersecretion and the medical consequences. With current therapeutic options, successful disease control should be achieved in the majority of patients. ■

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