Diagnosis and Management of Acromegaly in 2014 (Update from 2012)

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Abstract

In this update to the 2012 summary, the current diagnostic and therapeutic approaches to acromegaly are reviewed. The goals of therapy are to control excess growth hormone (GH) secretion and tumor growth, and to limit, if not reverse, the long-term medical consequences and risk for 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. Use of a somatostatin receptor ligand (SRL) preoperatively to improve surgical outcomes has not been substantiated. Medical therapy, including SRLs, 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 SRLs. 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. Because tumors 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 comorbidities, and accompanying clinical features. Medical comorbidites include arthropathy, cardiomegaly, type 2 diabetes, hypertension, sleep apnea syndrome, 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 comorbidities and reversal of the premature mortality risk. This current review is an update to the 2012 summary.[1]

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 amenorrhea.[2]

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 the recent Endocrine Society guidelines on the approach to acromegaly, it was recommended that a serum IGF-1 level be measured in subjects with acral manifestations. Owing to the lack of agreement between assays and the lack of validated normal ranges for IGF-1,[3,4] the same assay should be used in the same patient for serial measurement.[5] A random GH measurement was not 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. Additionally, in subjects with elevated or equivocal serum IGF-1 concentrations, the recent acromegaly guidelines recommended confirmation of the diagnosis with a lack of suppression of GH to less than 1 mcg/l following an oral glucose load.[6] In a patient with signs and symptoms of acromegaly and an elevated IGF-1 value, an oral glucose tolerance test (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.[7]

After diagnosis of acromegaly, a magnetic resonance imaging (MRI) scan of the sella should be obtained to determine tumor size, location, and invasiveness.[6] Visual field testing is performed if the tumor is touching or compressing the optic chiasm. A thorough ophthalmologic examination should be performed if the patient describes diplopia and the tumor is invading the cavernous sinus. Further endocrine testing should be performed to determine general pituitary function and need for hormone replacement therapy.

Management of Medical Comorbidities

Acromegaly is associated with diabetes, hypertension, sleep apnea syndrome, and cardio and cerebrovascular disease. These comorbidities should be

monitored longitudinally and managed appropriately. Because a recent meta-analysis showed that the risk for colonic polyps is increased in acromegaly,[8] colonoscopy is suggested at diagnosis in a patient with acromegaly.[6] Also, acromegaly is associated with an increase in thyroid nodules and thyroid cancer.[9] The recent acromegaly guidelines suggested that a thyroid ultrasound be performed if there is palpable thyroid nodularity.[6]

Treatment

The goals of therapy for acromegaly are to control GH and IGF-1 activity, reduce tumor size and prevent local mass effects, reduce signs and symptoms of disease, prevent or improve medical comorbidities, 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 useful to debulk or resect the somatotroph adenoma, decompress local mass effects, rapidly lower or normalize GH and IGF-1 values, and obtain pathologic tissue for further analysis. Surgery is recommended for all subjects with microadenomas because approximately 80 % or more of microadenomas are curable.[10] 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.[9,11–13] 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 use of primary medical therapy alone.[14] 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.[12]

Postoperative Assessment

Surgical efficacy is assessed by measuring an IGF-1 level and a random GH at 12 weeks or later.[9] Although GH levels may be performed as early as postoperative day 1 and may correlate with subsequent IGF-1 levels, the role of the early GH value is limited as an elevated value may reflect surgical stress. An oral glucose tolerance with a level less than 1 mcg/l also indicated biochemical control, and a random serum GH <0.14 mcg/l suggests remission as well.[6,15] 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 edema and involution of Gelfoam® and fat packing.[16] Repeat pituitary hormone studies are performed at this time as well to assess for residual function.

Is There a Role for Preoperative Medical Therapy?

A role for medical therapy, particularly with somatostatin receptor ligands (SRLs), to improve surgical remission has been considered. Controlled prospective studies showed that up to 6 months of preoperative SRLs resulted in improved surgical outcomes, especially in patients with macroadenomas.[17–19] Limitations of these studies include low remission rates in the groups randomized to surgery alone, as well as a possible carryover effect of the preoperative SRLs on the 12-week postoperative IGF-1 levels. In a follow-up study of 62 patients randomized to SRLs prior to surgery versus surgery alone, there was no significant difference in biochemical control by 1 year.[20] Therefore, current guidelines do not support routine use of a SRL with goal to improve surgical outcome.[6]

Another consideration is the use of medical therapy preoperatively to improve anesthetic risk in the peri- and postoperative settings. Because intubation may be difficult and traumatic in up to 30 % of acromegaly patients, a role for medical therapy to reduce soft tissue swelling and reduce this risk has been considered.[21] In addition, subjects with acromegaly are at risk for cardiovascular disease, including hypertension and hypertrophic cardiomyopathy, with associated reduced ejection fraction.[22] Medical therapy may improve cardiovascular morbidities and surgical outcomes.[22–24] 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.[25] 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 tumor debulking to improve response to medical therapy.[14]

Biochemical Assessment for Determining Efficacy of Medical Therapy

For SRL 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.[6] The use of measurement of GH suppression following glucose administration to monitor efficacy of medical therapy is unclear.[26] With administration of pegvisomant, serum IGF-1 should only 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.[27,28]

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 normalizes IGF-1 levels in approximately 8 % of patients and high doses are often required.[29] 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.[30,31] 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.[32,33] 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 for echocardiographic valvular abnormalities.[34] 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 Receptor Ligands

SRLs are the mainstay of medical therapy for acromegaly and are highly effective at improving both biochemical parameters and medical comorbidities. There are two available SRL 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 2 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.[35] 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 % normalization of GH and 67 % normalization of IGF-I levels.[36] Octreotide LAR and lanreotide autogel have similar pharmacologic and efficacy profiles.[37] SRL administration to both SRL in both drug-naïve and postoperative patients results in IGF-1 control is approximately 17–35 %.[38,39] In a recent study, 63 % of patients had significant tumor shrinkage, and 54 % had shrinkage within 12 weeks.[38] The efficacy of SRLs is a function of the somatostatin receptor subtype 2 density, although the presence of receptor subtypes is not routinely assessed.[40] Response to SRLs is inversely correlated with tumor size and degree of GH hypersecretion. In cases where IGF-1 levels fall excessively, SRLs may be administered at 6-week intervals or longer. The acute GH reduction following a single subcutaneous dose of octreotide and the degree of radiolabeled octreotide uptake has not been shown to be accurate in predicting biochemical remission.[41]

Pegvisomant

Pegvisomant is a recombinantly derived analog of human GH that acts as a highly selective GH receptor antagonist.[27,28] 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 the pivotal study involving a double-blind, placebo-controlled 12-week trial, daily subcutaneous administration of pegvisomant normalized IGF-1 in 89 % of cases.[27,28] In a recently published surveillance study involving 1,288 patients, pegvisomant administration resulted in IGF-1 control in 63 % of patients.[42] In a more recent study, pegvisomant resulted in biochemical control in 31 % of subjects.[39] These efficacy discrepancies likely reflect 'real life' compliance challenges as well as inadequate dose titration compared with a controlled trial environment. Given efficacy of pegvisomant, a recent guideline has suggested that pegvisomant may be considered as the initial option for adjuvant medical therapy in patients who have residual disease following surgery.[6] In patients controlled with daily pegvisomant, conversion to a once- or twice-weekly dose regiment can be considered: less frequent administration may be preferred.[43] Tumor growth may occur in 3–5 % of subjects, though it is unclear whether this reflects the natural history of adenoma growth or loss of IGF-1 feedback.[44,45] It is recommended that patients undergo monitoring with serial MRI scans; for example, at 6-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.[46] These transaminase elevations are usually asymptomatic and often transient and self-limiting, despite continued administration of pegvisomant.[46] Regular monitoring of liver function tests is recommended with discontinuation of the drug if these abnormalities are significantly elevated, such as greater than three times normal. Additional and uncommon adverse effects include an influenza-like illness, local allergic reactions, and local lipohypertrophy.[47]

How to Manage the Patient with Somatostatin Analog Resistance?

There are several management options for patients who are resistant to SRLs. One option is to increase the SRL 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.[48] In a patient with partial SRL resistance, either pegvisomant or cabergoline could be added to the SRL for additive effect. For example, the addition of pegvisomant to a SRL may result in biochemical control in up to 58 % of subjects and, through dose reduction of both the pegvisomant and SRL, this regimen may have a cost benefit.[49] Addition of cabergoline to patients with partial response to a SRL may lead to IGF-1 normalization in about half of subjects,[50] 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 SRLs.[51] In a patient with full resistance to a SRL, substitution of pegvisomant for the SRL may be considered.[52] Finally, in a patient with SRL resistance, consideration of radiation therapy may be warranted.[5]

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.[53–55] There are two main types of radiotherapy for patients with acromegaly: conventional fractionated radiotherapy and stereotactic radiosurgery.

Stereotactic radiosurgery includes a number of modalities, such as Gamma Knife, CyberKnife, and a linear accelerator that delivers high-energy photons. Another option is use of proton particles.[56] 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 10–60 % over a 5-year follow-up period.[57–59] It has been suggested that time to remission is shorter with Gamma Knife radiosurgery than with conventional radiotherapy, although this is not entirely clear.[57,59]

Radiosurgery is generally considered if the tumor is a minimal distance from the optic chiasm resulting in an exposure of more than 800 cGy.[60] Periodic withdrawal of medical therapy following radiotherapy should be performed for biochemical assessment.[6] SRLs 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.[57,59,61]

The main limitation for radiotherapy is the development of hypopituitarism, which may occur in up to 50 % of patients after 5 to 10 years.[62,63] Radiation-induced secondary tumors and radionecrosis have been reported in fewer than 2 % of patients undergoing conventional radiotherapy.[64,65]

Conclusion

This summary serves as an update to the 2012 review.[1] In this update, the current approach to both diagnosis and therapy of acromegaly is reviewed. Surgery is the initial approach in the majority of patients. As surgical debulking can improve subsequent response to medical therapy, surgery should be considered in subjects with low likelihood of cure given parasellar invasion by the tumor. Medical therapy, either as mono or combination therapy, is effective in most patients with residual disease following incomplete surgery. In addition, primary medical therapy with a SRL has a role in selected patients. ■

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